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(54) Title: INHIBITION OF p38 KINASE ACTIVITY USING SUBSTITUTED HETEROCYCLIC UREAS

(57) Abstract

This invention relates to the use of a group of aryl ureas in treating cytokine mediated diseases, other than cancer and proteolytic enzyme mediated diseases, other than cancer, and pharmaceutical compositions for use in such therapy.

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Inhibition of p38 Kinase Activity Using Substituted Heterocyclic Ureas

Field of the Invention

This invention relates to the use of a group of aryl ureas in treating cytokine mediated diseases and proteolytic enzyme mediated diseases, and pharmaceutical compositions for use in such therapy.

Background of the Invention

Two classes of effector molecules which are critical for the progression of rheumatoid arthritis are pro-inflammatory cytokines and tissue degrading proteases. Recently, a family of kinases was described which is instrumental in controlling the transcription and translation of the structural genes coding for these effector molecules.

The mitogen-activated protein (MAP) kinase family is made up of a series of structurally related proline-directed serine/threonine kinases which are activated either by growth factors (such as EGF) and phorbol esters (ERK), or by IL-1, TNFα or stress (p38, JNK). The MAP kinases are responsible for the activation of a wide variety of transcription factors and proteins involved in transcriptional control of cytokine production. A pair of novel protein kinases involved in the regulation of cytokine synthesis was recently described by a group from SmithKline Beecham (Lee et al. *Nature* **1994**, *372*, 739). These enzymes were isolated based on their affinity to bond to a class of compounds, named CSAIDSs (cytokine suppressive anti-inflammatory drugs) by SKB. The CSAIDs, bicyclic pyridinyl imidazoles, have been shown to have cytokine inhibitory activity both *in vitro* and *in vivo*. The isolated enzymes, CSBP-1 and -2 (CSAID binding protein 1 and 2) have been cloned and expressed. A murine homologue for CSBP-2, p38, has also been reported (Han et al. *Science* **1994**, *265*, 808).

Early studies suggested that CSAIDs function by interfering with m-RNA translational events during cytokine biosynthesis. Inhibition of p38 has been shown to inhibit both cytokine production (eg., TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (eg., MMP-1, MMP-3) *in vitro* and/or *in vivo*.

Clinical studies have linked TNFα production and/or signaling to a number of diseases including rheumatoid arthritis (Maini. *J. Royal Coll. Physicians London* **1996**, *30*, 344). In addition, excessive levels of TNFα have been implicated in a wide variety of inflammatory and/or immunomodulatory diseases, including acute rheumatic fever (Yegin et al. *Lancet* **1997**, *349*, 170), bone resorption (Pacifici et al. *J. Clin. Endocrinol. Metabol.* **1997**, *82*, 29), postmenopausal osteoperosis (Pacifici et al. *J. Bone Mineral Res.* **1996**, *11*, 1043), sepsis (Blackwell et al. *Br. J. Anaesth.* **1996**, *77*, 110), gram negative sepsis (Debets et al. *Prog. Clin. Biol. Res.* **1989**, *308*, 463), septic shock (Tracey et al. *Nature* **1987**, *330*, 662; Girardin et al. *New England J. Med.* **1988**, *319*, 397), endotoxic shock (Beutler et al. *Science* **1985**, *229*, 869; Ashkenasi et al. *Proc. Nat'l. Acad. Sci. USA* **1991**, *88*, 10535), toxic shock syndrome, (Saha et al. *J. Immunol.* **1996**, *157*, 3869; Lina et al. *FEMS Immunol. Med. Microbiol.* **1996**, *13*, 81), systemic inflammatory response syndrome (Anon. *Crit. Care Med.* **1992**, *20*, 864), inflammatory bowel diseases (Stokkers et al. *J. Inflamm.* **1995-6**, *47*, 97) including Crohn's disease (van Deventer et al. *Aliment. Pharmacol. Therapeu.* **1996**, *10 (Suppl. 2)*, 107; van Dullemen et al. *Gastroenterology* **1995**, *109*, 129) and ulcerative colitis (Masuda et al. *J. Clin. Lab. Immunol.* **1995**, *46*, 111), Jarisch-Herxheimer reactions (Fekade et al. *New England J. Med.* **1996**, *335*, 311), asthma (Amrani et al. *Rev. Malad. Respir.* **1996**, *13*, 539), adult respiratory distress syndrome (Roten et al. *Am. Rev. Respir. Dis.* **1991**, *143*, 590; Suter et al. *Am. Rev. Respir. Dis.* **1992**, *145*, 1016), acute pulmonary fibrotic diseases (Pan et al. *Pathol. Int.* **1996**, *46*, 91), pulmonary sarcoidosis (Ishioka et al. *Sarcoidosis Vasculitis Diffuse Lung Dis.* **1996**, *13*, 139), allergic respiratory diseases (Casale et al. *Am. J. Respir. Cell Mol. Biol.* **1996**, *15*, 35), silicosis (Gossart et al. *J. Immunol.* **1996**, *156*, 1540; Vanhee et al. *Eur. Respir. J.* **1995**, *8*, 834), coal worker's pneumoconiosis (Borm et al. *Am. Rev. Respir. Dis.* **1988**, *138*, 1589), alveolar injury (Horinouchi et al. *Am. J. Respir. Cell Mol. Biol.* **1996**, *14*, 1044), hepatic failure (Gantner et al. *J. Pharmacol. Exp. Therap.*

1997, *280*, 53), liver disease during acute inflammation (Kim et al. *J. Biol. Chem.* 1997, *272*, 1402), severe alcoholic hepatitis (Bird et al. *Ann. Intern. Med.* 1990, *112*, 917), malaria (Grau et al. *Immunol. Rev.* 1989, *112*, 49; Taverne et al. *Parasitol. Today* 1996, *12*, 290) including Plasmodium falciparum malaria (Perlmann et al. *Infect. Immunit.* 1997, *65*, 116) and cerebral malaria (Rudin et al. *Am. J. Pathol.* 1997, *150*, 257), non-insulin-dependent diabetes mellitus (NIDDM; Stephens et al. *J. Biol. Chem.* 1997, *272*, 971; Ofei et al. *Diabetes* 1996, *45*, 881), congestive heart failure (Doyama et al. *Int. J. Cardiol.* 1996, *54*, 217; McMurray et al. *Br. Heart J.* 1991, *66*, 356), damage following heart disease (Malkiel et al. *Mol. Med. Today* 1996, *2*, 336), atherosclerosis (Parums et al. *J. Pathol.* 1996, *179*, A46), Alzheimer's disease (Fagarasan et al. *Brain Res.* 1996, *723*, 231; Aisen et al. *Gerontology* 1997, *43*, 143), acute encephalitis (Ichiyama et al. *J. Neurol.* 1996, *243*, 457), brain injury (Cannon et al. *Crit. Care Med.* 1992, *20*, 1414; Hansbrough et al. *Surg. Clin. N. Am.* 1987, *67*, 69; Marano et al. *Surg. Gynecol. Obstetr.* 1990, *170*, 32), multiple sclerosis (M.S.; Coyle. *Adv. Neuroimmunol.* 1996, *6*, 143; Matusevicius et al. *J. Neuroimmunol.* 1996, *66*, 115) including demyelation and oligiodendrocyte loss in multiple sclerosis (Brosnan et al. *Brain Pathol.* 1996, *6*, 243), advanced cancer (MucWierzgon et al. *J. Biol. Regulators Homeostatic Agents* 1996, *10*, 25), lymphoid malignancies (Levy et al. *Crit. Rev. Immunol.* 1996, *16*, 31), pancreatitis (Exley et al. *Gut* 1992, *33*, 1126) including systemic complications in acute pancreatitis (McKay et al. *Br. J. Surg.* 1996, *83*, 919), impaired wound healing in infection inflammation and cancer (Buck et al. *Am. J. Pathol.* 1996, *149*, 195), myelodysplastic syndromes (Raza et al. *Int. J. Hematol.* 1996, *63*, 265), systemic lupus erythematosus (Maury et al. *Arthritis Rheum.* 1989, *32*, 146), biliary cirrhosis (Miller et al. *Am. J. Gasteroenterolog.* 1992, *87*, 465), bowel necrosis (Sun et al. *J. Clin. Invest.* 1988, *81*, 1328), psoriasis (Christophers. *Austr. J. Dermatol.* 1996, *37*, S4), radiation injury (Redlich et al. *J. Immunol.* 1996, *157*, 1705), and toxicity following administration of monoclonal antibodies such as OKT3 (Brod et al. *Neurology* 1996, *46*, 1633). TNFα levels have also been related to host-versus-graft reactions (Piguet et al. *Immunol. Ser.* 1992, *56*, 409) including ischemia reperfusion injury (Colletti et al. *J. Clin. Invest.* 1989, *85*, 1333) and allograft rejections including those of the kidney (Maury et al. *J. Exp. Med.* 1987, *166*, 1132), liver (Imagawa et al. *Transplantation* 1990, *50*, 219), heart (Bolling et al. *Transplantation* 1992, *53*, 283), and skin (Stevens et al.

Transplant. Proc. **1990**, *22*, 1924), lung allograft rejection (Grossman et al. *Immunol. Allergy Clin. N. Am.* **1989**, *9*, 153) including chronic lung allograft rejection (obliterative bronchitis; LoCicero et al. *J. Thorac. Cardiovasc. Surg.* **1990**, *99*, 1059), as well as complications due to total hip replacement (Cirino et al. *Life Sci.* **1996**, *59*, 86). TNFα has also been linked to infectious diseases (review: Beutler et al. *Crit. Care Med.* **1993**, *21*, 5423; Degre. *Biotherapy* **1996**, *8*, 219) including tuberculosis (Rook et al. *Med. Malad. Infect.* **1996**, *26*, 904), Helicobacter pylori infection during peptic ulcer disease (Beales et al. *Gastroenterology* **1997**, *112*, 136), Chaga's disease resulting from Trypanosoma cruzi infection (Chandrasekar et al. *Biochem. Biophys. Res. Commun.* **1996**, *223*, 365), effects of Shiga-like toxin resulting from E. coli infection (Harel et al. *J. Clin. Invest.* **1992**, *56*, 40), the effects of enterotoxin A resulting from Staphylococcus infection (Fischer et al. *J. Immunol.* **1990**, *144*, 4663), meningococcal infection (Waage et al. *Lancet* **1987**, 355; Ossege et al. *J. Neurolog. Sci.* **1996**, *144*, 1), and infections from Borrelia burgdorferi (Brandt et al. *Infect. Immunol.* **1990**, *58*, 983), Treponema pallidum (Chamberlin et al. *Infect. Immunol.* **1989**, *57*, 2872), cytomegalovirus (CMV; Geist et al. *Am. J. Respir. Cell Mol. Biol.* **1997**, *16*, 31), influenza virus (Beutler et al. *Clin. Res.* **1986**, *34*, 491a), Sendai virus (Goldfield et al. *Proc. Nat'l. Acad. Sci. USA* **1989**, *87*, 1490), Theiler's encephalomyelitis virus (Sierra et al. *Immunology* **1993**, *78*, 399), and the human immunodeficiency virus (HIV; Poli. *Proc. Nat'l. Acad. Sci. USA* **1990**, *87*, 782; Vyakaram et al. *AIDS* **1990**, *4*, 21; Badley et al. *J. Exp. Med.* **1997**, *185*, 55).

Because inhibition of p38 leads to inhibition of TNFα production, p38 inhibitors will be useful in treatment of the above listed diseases.

A number of diseases are thought to be mediated by excess or undesired matrix-destroying metalloprotease (MMP) activity or by an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. *J. Biol. Chem.* **1984**, *259*, 3633), rheumatoid arthritis (Mullins et al. *Biochim. Biophys. Acta* **1983**, *695*, 117; Woolley et al. *Arthritis Rheum.* **1977**, *20*, 1231; Gravallese et al. *Arthritis Rheum.* **1991**, 34, 1076), septic arthritis (Williams et al. *Arthritis Rheum.* **1990**, *33*, 533), tumor metastasis (Reich et al. *Cancer Res.* **1988**, *48*, 3307; Matrisian et al. *Proc. Nat'l. Acad. Sci., USA* **1986**, *83*,

9413), periodontal diseases (Overall et al. *J. Periodontal Res.* **1987**, *22*, 81), corneal ulceration (Burns et al. *Invest. Opthalmol. Vis. Sci.* **1989**, *30*, 1569), proteinuria (Baricos et al. *Biochem. J.* **1988**, *254*, 609), coronary thrombosis from atherosclerotic plaque rupture (Henney et al. *Proc. Nat'l. Acad. Sci., USA* **1991**, *88*, 8154), aneurysmal aortic disease (Vine et al. *Clin. Sci.* **1991**, *81*, 233), birth control (Woessner et al. *Steroids* **1989**, *54*, 491), dystrophobic epidermolysis bullosa (Kronberger et al. *J. Invest. Dermatol.* **1982**, *79*, 208), degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease, and demyelating diseases of the nervous system (Chantry et al. *J. Neurochem.* **1988**, *50*, 688).

Because inhibition of p38 leads to inhibition of MMP production, p38 inhibitors will be useful in treatment of the above listed diseases.

Inhibitors of p38 are active in animal models of TNFα production, including a muirne lipopolysaccharide (LPS) model of TNFα production. Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Fruend's adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes.

The need for new therapies is especially important in the case of arthritic diseases. The primary disabling effect of osteoarthritis, rheumatoid arthritis and septic arthritis is the progressive loss of articular cartilage and thereby normal joint function. No marketed pharmaceutical agent is able to prevent or slow this cartilage loss, although nonsteroidal antiinflammatory drugs (NSAIDs) have been given to control pain and swelling. The end result of these diseases is total loss of joint function which is only treatable by joint replacement surgery. P38 inhibitors will halt or reverse the progression of cartilage loss and obviate or delay surgical intervention.

Several patents have appeared claiming polyarylimidazoles and/or compounds containing polyarylimidazoles as inhibitors of p38 (for example, Lee et al. WO 95/07922; Adams et al. WO 95/02591; Adams et al. WO 95/13067; Adams et al. WO 95/31451). It has been reported that arylimidazoles complex to the ferric form of cytochrome $P450_{cam}$ (Harris et al. *Mol. Eng.* **1995**, *5*, 143, and references therein), causing concern that these compounds may display structure-related toxicity (Howard-Martin et al. *Toxicol. Pathol.* **1987**, *15*, 369). Therefore, there remains a need for improved p38 inhibitors.

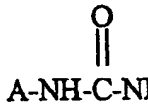
Summary of the Invention

This invention provides compounds, generally described as aryl ureas, including both aryl and heteroaryl analogues, which inhibit p38 mediated events and thus inhibit the production of cytokines (such as TNFα, IL-1 and IL-8) and proteolytic enzymes (such as MMP-1 and MMP-3). The invention also provides a method of treating a cytokine mediated disease state in humans or mammals, wherein the cytokine is one whose production is affected by p38. Examples of such cytokines include, but are not limited to TNFα, IL-1 and IL-8. The invention also provides a method of treating a protease mediated disease state in humans or mammals, wherein the protease is one whose production is affected by p38. Examples of such proteases include, but are not limited to collagenase (MMP-1) and stromelysin (MMP-3).

Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid arthritis, osteoarthritis, septic arthritis, rheumatic fever, bone resorption, postmenopausal osteoperosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic diseases, pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including Plasmodium falciparum malaria and cerebral malaria, non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's

disease, acute encephalitis, brain injury, multiple sclerosis including demyelation and oligiodendrocyte loss in multiple sclerosis, advanced cancer, lymphoid malignancies, tumor metastasis, pancreatitis, including systemic complications in acute pancreatitis, impaired wound healing in infection, inflammation and cancer, periodontal diseases, corneal ulceration, proteinuria, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies such as OKT3, host-versus-graft reactions including ischemia reperfusion injury and allograft rejections including kidney, liver, heart, and skin allograft rejections, lung allograft rejection including chronic lung allograft rejection (obliterative bronchitis) as well as complications due to total hip replacement, and infectious diseases including tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

Accordingly, the present invention is directed to a method for the treatment of diseases mediated by one or more cytokine or proteolytic enzyme produced and/or activated by a p38 mediated process, comprising administering a compound of formula I



I

wherein B is generally an unsubstituted or substituted, up to tricyclic, aryl or heteroaryl moiety with up to 30 carbon atoms with at least one 5 or 6 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur. A is a heteroaryl moiety discussed in more detail below.

The aryl and heteroaryl moiety of B may contain separate cyclic structures and can include a combination of aryl, heteroaryl and cycloalkyl structures. The substituents for these aryl and heteroaryl moieties can vary widely and include halogen, hydrogen, hydrosulfide, cyano, nitro, amines and various carbon-based moieties, including those

which contain one or more of sulfur, nitrogen, oxygen and/or halogen and are discussed more particularly below.

Suitable aryl and heteroaryl moieties for B of formula I include, but are not limited to aromatic ring structures containing 4-30 carbon atoms and 1-3 rings, at least one of which is a 5-6 member aromatic ring. One or more of these rings may have 1-4 carbon atoms replaced by oxygen, nitrogen and/or sulfur atoms.

Examples of suitable aromatic ring structures include phenyl, pyridinyl, naphthyl, pyrimidinyl, benzothiazolyl, quinoline, isoquinoline, phthalimidinyl and combinations thereof, such as diphenyl ether (phenyloxyphenyl), diphenyl thioether (phenylthiophenyl), diphenyl amine (phenylaminophenyl), phenylpyridinyl ether (pyridinyloxyphenyl), pyridinylmethylphenyl, phenylpyridinyl thioether (pyridinylthiophenyl), phenylbenzothiazolyl ether (benzothiazolyloxyphenyl), phenylbenzothiazolyl thioether (benzothiazolylthiophenyl), phenylpyrimidinyl ether, phenylquinoline thioether, phenylnaphthyl ether, pyridinylnapthyl ether, pyridinylnaphthyl thioether, and phenylphthalimidylmethyl.

Examples of suitable heteroaryl groups include, but are not limited to, 5-12 carbon-atom aromatic rings or ring systems containing 1-3 rings, at least one of which is aromatic, in which one or more, e.g., 1-4 carbon atoms in one or more of the rings can be replaced by oxygen, nitrogen or sulfur atoms. Each ring typically has 3-7 atoms. For example, B can be 2- or 3-furyl, 2- or 3-thienyl, 2- or 4-triazinyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 1,2,3-triazol-1-, -4- or –5-yl, 1,2,4-triazol-1-, -3- or –5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or –5-yl, 1,2,4-oxadiazol-3- or –5-yl, 1,3,4-thiadiazol-2- or –5-yl, 1,2,4-oxadiazol-3- or –5-yl, 1,3,4-thiadiazol-2- or –5-yl, 1,3,4-thiadiazol-3- or –5-yl, 1,2,3-thiadiazol-4- or –5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5- 6- or 7-benzisoxazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benz-1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-

quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, 8- isoquinolinyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, or 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, or additionally optionally substituted phenyl, 2- or 3-thienyl, 1,3,4-thiadiazolyl, 3-pyrryl, 3-pyrazolyl, 2-thiazolyl or 5-thiazolyl, etc. For example, B can be 4-methyl-phenyl, 5-methyl-2-thienyl, 4-methyl-2-thienyl, 1-methyl-3-pyrryl, 1-methyl-3-pyrazolyl, 5-methyl-2-thiazolyl or 5-methyl-1,2,4-thiadiazol-2-yl.

Suitable alkyl groups and alkyl portions of groups, e.g., alkoxy, etc. throughout include methyl, ethyl, propyl, butyl, etc., including all straight-chain and branched isomers such as isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, etc.

Suitable aryl groups include, for example, phenyl and 1- and 2-naphthyl.

Suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclohexyl, etc. The term "cycloalkyl", as used herein, refers to cyclic structures with or without alkyl substituents such that, for example, "C_4 cycloalkyl" includes methyl substituted cyclopropyl groups as well as cyclobutyl groups. The term "cycloalkyl" also includes saturated heterocyclic groups.

Suitable halogens include F, Cl, Br, and/or I, from one to persubstitution (i.e., all H atoms on the group are replaced by halogen atom), being possible, mixed substitution of halogen atom types also being possible on a given moiety.

As indicated above, these ring systems can be unsubstituted or substituted by substituents such as halogen up to per-halosubstitution. Other suitable substituents for the moieties of B include alkyl, alkoxy, carboxy, cycloalkyl, aryl, heteroaryl, cyano, hydroxy and amine. These other substituents, generally referred to as X and X' herein, include –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar.

Where a substituent, X or X', is a substituted group, it is preferably substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$,

$-NR^5C(O)OR^{5'}$ and halogen up to per-halo substitution.

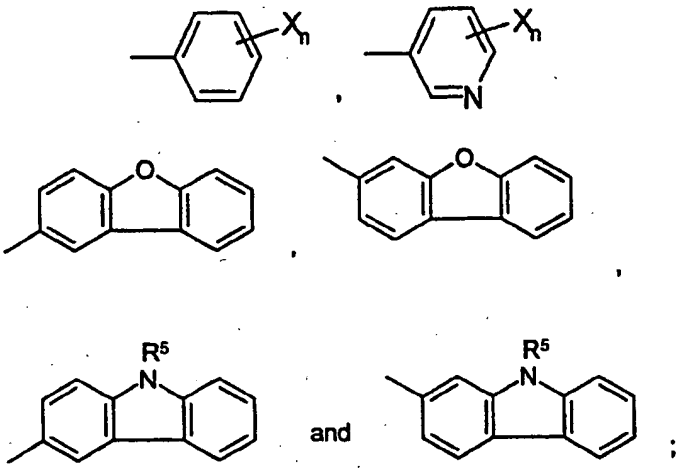
The moieties R^5 and $R^{5'}$ are preferably independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_2-C_{10} alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl.

The bridging group Y is preferably -O-, -S-, $-N(R^5)-$, $-(CH_2)_m-$, -C(O)-, $-NR^5C(O)NR^5R^{5'}$, $-NR^5C(O)-$, $-C(O)NR^5$, -CH(OH)-, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$, where m = 1-3, and X^a is halogen.

The moiety Ar is preferably a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3.

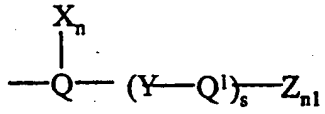
Each Z substituent is preferably independently selected from the group consisting of –CN, $-CO_2R^5$, =O, $-C(O)NR^5R^{5'}$, $-C(O)-NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-C(O)R^5$, $-NR^5C(O)R^{5'}$, $-SO_2R^5$, $-SO_2NR^5R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl. If Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, =O, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C-C_{10} heteroaryl, C_6-C_{14} aryl, C_4-C_{24} alkheteroaryl and C_7-C_{24} alkaryl.

The aryl and heteroaryl moieties of B of Formula I are preferably selected from the group consisting of



which are unsubstituted or substituted by halogen, up to per-halosubstitution. X is as defined above and n = 0-3.

The aryl and heteroaryl moieties of B are more preferably of the formula II:



II

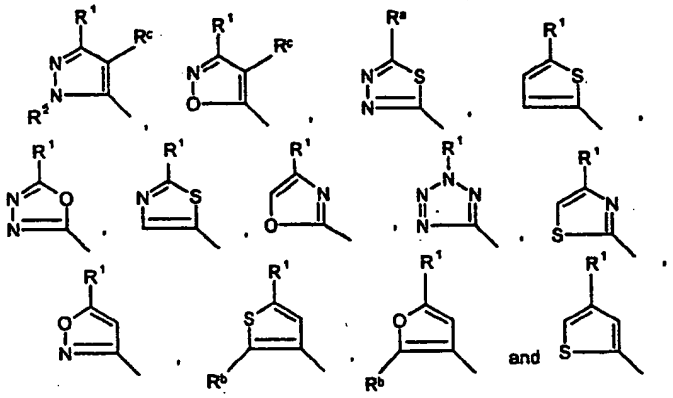
wherein Y is selected from the group consisting of –O-, -S-, $-CH_2-$, $-SCH_2-$, $-CH_2S-$, -CH(OH)-, -C(O)-, $-CX^a_2-$, $-CX^aH-$, $-CH_2O-$ and $-OCH_2-$ and X^a is halogen.

Q is a six member aromatic structure containing 0–2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution and Q^1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution. X, Z, n and n1 are as defined above and s = 0 or 1.

In preferred embodiments, Q is phenyl or pyridinyl, substituted or unsubstituted by halogen, up to per-halosubstitution and Q^1 is selected from the group consisting of

phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, or -Y-Q^1 is phthalimidinyl substituted or unsubstituted by halogen up to per-halo substitution. Z and X are preferably independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is preferably selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

The heteroaryl moiety A of formula I is preferably selected from the group consisting of:



The substituent R^1 preferably is selected from the group consisting of halogen, C_3-C_{10} alkyl, C_1-C_{13} heteroaryl, C_6-C_{14} aryl, C_7-C_{24} alkylaryl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} hetero, up to per-halosubstituted C_6-C_{13} aryl and up to per-halosubstituted C_7-C_{24} alkaryl.

The substituent R^2 is preferably selected from the group consisting of H, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^3R^{3'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl. Where R^2 is a substituted group, it is preferably substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^4$, $-C(O)-NR^3R^{3'}$, $-NO_2$, $-OR^4$, $-SR^4$, and halogen up to per-halosubstitution.

R^3 and $R^{3'}$ are preferably independently selected from the group consisting of H, $-OR^4$, $-SR^4$, $-NR^4R^{4'}$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^4R^{4'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl.

R^4 and $R^{4'}$ are preferably independently selected from the group consisting of H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl; C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl.

R^a is preferably C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl.

R^b is preferably hydrogen or halogen.

R^c is hydrogen, halogen, C_1-C_{10} alkyl, up to per-halosubstituted C_1-C_{10} alkyl or combines with R^1 and the ring carbon atoms to which R^1 and R^c are bound to form a 5- or 6-membered cycloalkyl, aryl or heteroaryl ring with 0-2 members selected from O, N and S.

Preferred pyrazolyl ureas include those wherein B is 2,3-dichlorophenyl or of the formula II above, wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y ix –O-, -S-, $-CH_2$ or $–SCH_2$, X is CF_3, Z is OH, Cl or $–NHC(O)-C_pH_{2p+1}$, wherein p = 2-4, s = 0 or 1, n = 0 or 1 and n1 = 0 or 1. Particular preferred pyrazolyl ureas include:

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(2,3-dichlorophenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-hydroxyphenyl)-thiophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-ethylaminocarbonylphenyl)-oxyphenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-isobutylaminocarbonyl-phenyl)-thiophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)thio-3-(trifluoromethyl)-phenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-((4-pyridinyl)methylthio)-phenyl)urea;

N-(1-(2,2,2-Trifluoroethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichloro-phenyl)urea;

N-(1-(2-Hydroxyethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-Ethoxycarbonylmethyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichloro-phenyl)urea;

N-(1-(2-Cyanoethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-(3-Hydroxyphenyl)methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)-urea;

N-(1-Cyclohexyl-3-*tert*-butyl-5-pyrazolyl)-n'-(4-(4-pyridinyl)methyl-phenyl)urea;

N-(1-methyl3-phenyl-5-pyrazolyl)-*N'*-(3-(4-(2-methylcarbamoyl)pyridyl)-thiophenyl) urea;

N-(1-methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridyl)thiophenyl) urea;

N-(1-methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(3-(4-pyridyl)thiophenyl) urea;

N-(1-methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(3-trifluoromethyl-4-(4-pyridylthio)phenyl) urea;

N-(3-*tert*-butyl-5-pyrazolyl)-*N'*-(3-(4-pyridyl)oxyphenyl) urea; and

N-(3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridyl)oxyphenyl) urea.

Preferred 5,3-isoxazolyl ureas wherein B is of the formula II above, wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is –O-, -S-, -CH_2, X is CF_3, Z is OH, CF_3 or

$-OC_pH_{2p+1}$, wherein p = 2-6, or $-C(O)-NH-CH_3$, s = 1, n = 0 or 1, and n is 0 or 1.

Particular preferred 5,3-isoxazolyl ureas include:

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-isopropoxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-isobutoxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pentyloxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-methylaminocarbonylphenyl)-oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)thio-3-(trifluoromethyl)-phenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(3-methyl-4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(3-methyl-4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-methyl-4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-methyl-4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-(2-methylcarbamoyl)pyridyl)-oxyphenyl) urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(3-(4-(2-methylcarbamoyl)pyridyl)-oxyphenyl) urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-(2-carbamoyl)pyridyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(3-(4-(2-carbamoyl)pyridyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(3-((4-pyridyl)fluoromethyl)phenyl) urea; and

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(3-((4-pyridyl)oxomethyl)phenyl) urea.

Preferred 3,5-isoxazolyl ureas include those wherein B is 2,3-dichlorophenyl or of the formula II above, wherein Q is phenyl, Q^1 is phenyl, pyridinyl or benzothiazolyl,

Y is –O-, -S-, -NH- or CH_2, Z is Cl, $–CH_3$- or $-OCH_3$, s = 0 or 1, n = 0 and n1 is 0 or 1. Particular preferred 3,5-isoxazolyl ureas include:

N-(3-Isopropyl -5-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-methoxyphenyl)aminophenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-methoxyphenyl)oxyphenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)methyl-phenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(4-(2-benzothiazolyl)oxy-phenyl)urea;

N-(3-(1-Methyl-1-ethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)-oxyphenyl)urea;

N-(3-(1-Methyl-1-ethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)methyl-phenyl)urea;

N-(3-cyclobutylyl-5-isoxazolyl)-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

N-(3-*tert*-butyl-5-isoxazolyl)-*N'*-(4-(4-pyridyl)thiophenyl) urea;

N-(3-(1-methyl-1-ethylprop-1-yl)-5-isoxazolyl)-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

N-(3-*tert*-butyl-5-isoxazolyl)-*N'*-(4-(4-pyridyl)methylphenyl) urea; and

N-(3-*tert*-butyl-5-isoxazolyl)-*N'*-(4-(4-methoxyphenyl)aminophenyl) urea.

Preferred thienyl ureas, furyl ureas and thiadiazolyl ureas include those wherein B is 2,3-dichlorophenyl of the formula II above, wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is –O-, -S- or $–CH_2$-, Z = CH_3, OH, Cl, $-O-C_2H_4$ or $–O-C_3H_7$, s = 0 or 1, n = 0 and n1 = 0 or 1. Preferred thienyl ureas include:

N-(2-Bromo-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-ethoxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-isopropoxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(3-pyridinyl)oxyphenyl)urea;

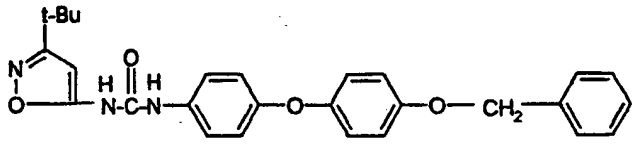
N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea; and

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea.

The invention also relates to which are within the scope of general formula I described above and more specifically include compounds of the formulae:

a)



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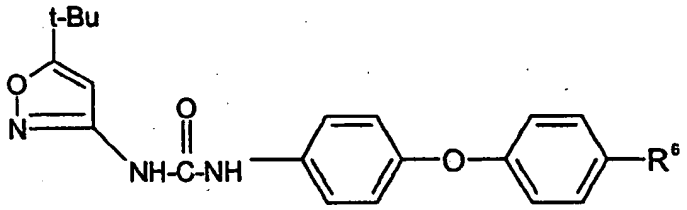
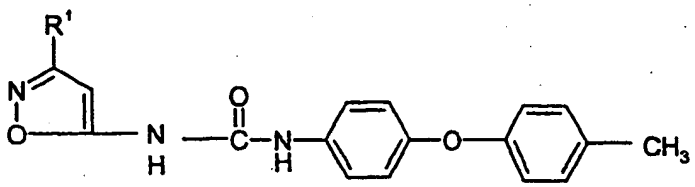
b)



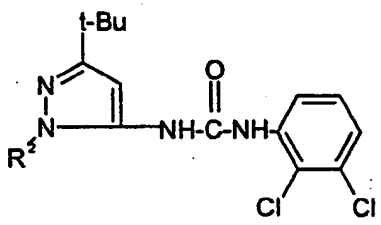
wherein R^6 is -O-CH_2–phenyl, -NH-C(O)-O-t-butyl, -O-n-pentyl , -O-n-butyl, -C(O)-$N(CH_3)_2$, -O-$CH_2CH(CH_3)_2$ or -O-n-propyl;

c)

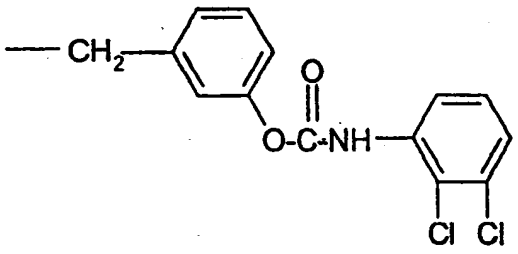


wherein R^1 is–CH_2-t-butyl;

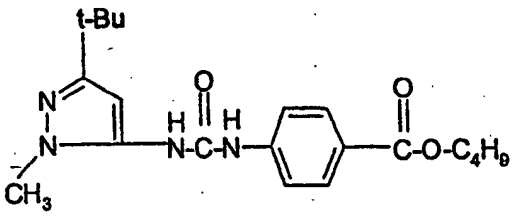
d)



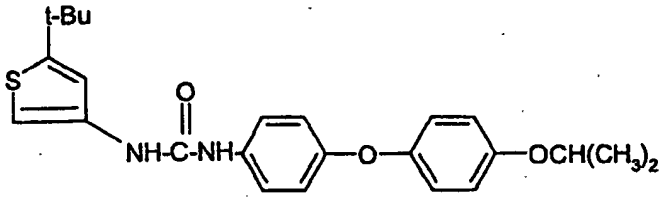
wherein R^2 is –CH_2–CF_3 , -C_2H_4-OH, –CH_2-(3-HOC_6H_4), –$CH_2C(O)NH_3$, –$CH_2C(O)OC_2H_5$, -C_2H_4CN, or



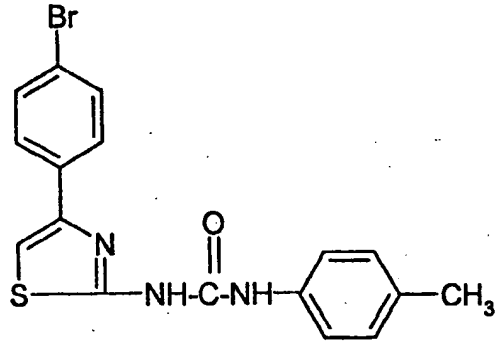
e)



f)

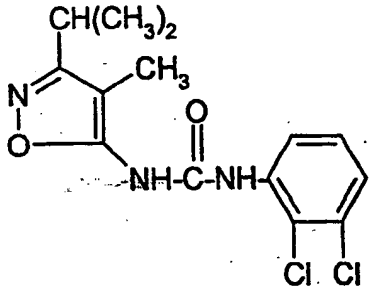


g)



and

h)



Preferred compounds also include the following thiadiazoles and thiophenes:

N-(5-*tert*-butyl-2-(1-thia-3,4-diazolyl))-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

N-(5-*tert*-butyl-2-(1-thia-3,4-diazolyl))-*N'*-(3-(4-pyridyl)thiophenyl) urea;

N-(5-*tert*-butyl-2-(1-thia-3,4-diazolyl))-*N'*-(3-(4-methoxyphenyl)oxyphenyl) urea;

N-(5-*tert*-butyl-2-(1-thia-3,4-diazolyl))-*N'*-(3-(4-methylphenyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-pyridyl)thiophenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-pyridyl)methylphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(2,3-dichlorophenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-methoxyphenyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-ethoxyphenyl)oxyphenyl) urea; and

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-isopropoxyphenyl)oxyphenyl) urea.

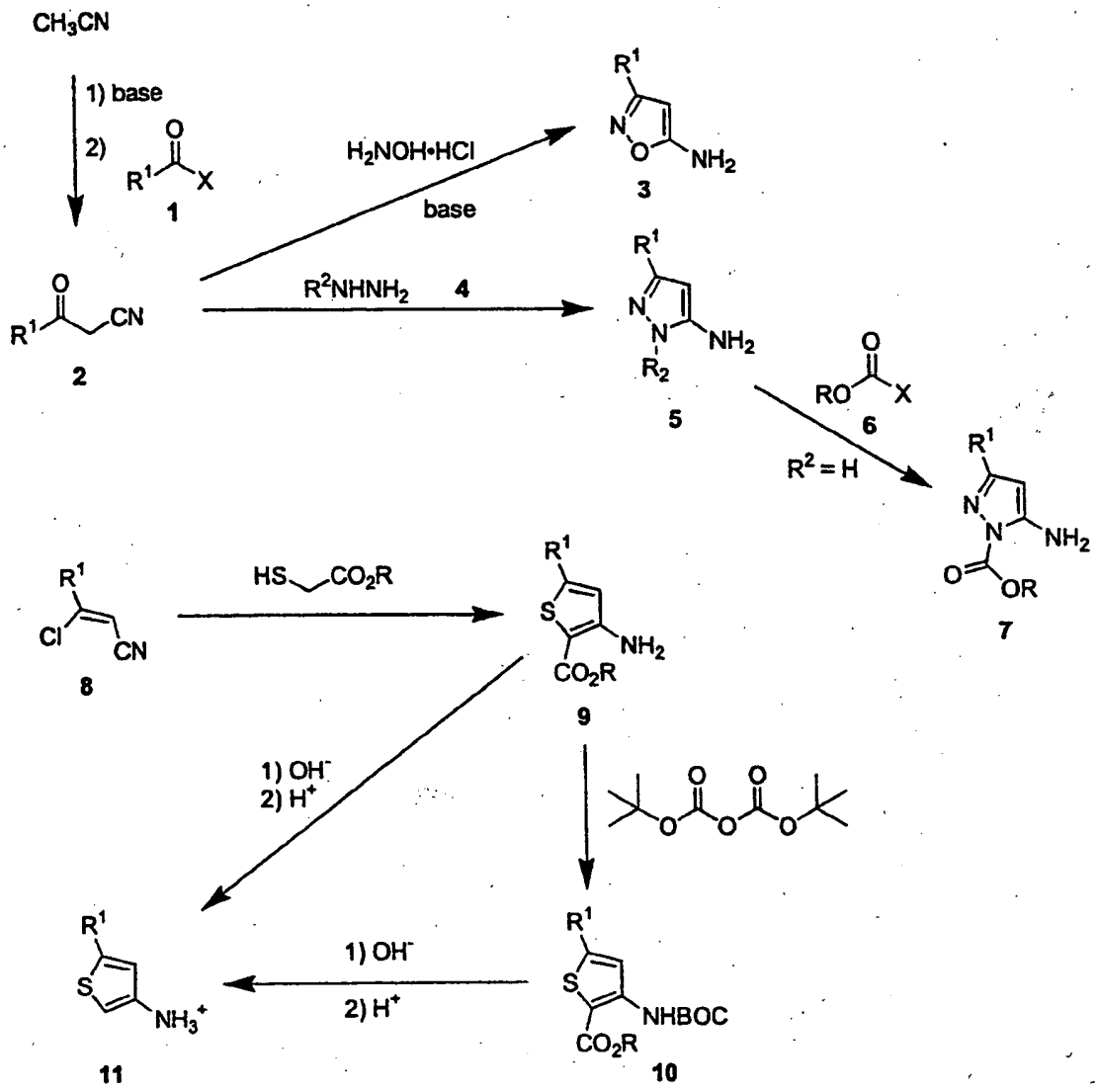
The present invention is also directed to pharmaceutically acceptable salts of formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, sulphonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2}, Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabiclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

A number of the compounds of Formula I possess asymmetric carbons and can therefore exist in racemic and optically active forms. Methods of separation of enantiomeric and diastereomeric mixtures are well known to one skilled in the art. The present invention encompasses any isolated racemic or optically active form of compounds described in Formula I which possess p38 kinase inhibitory activity.

General Preparative Methods

The compounds of Formula I may be prepared by use of known chemical reactions and procedures, some from starting materials which are commercially available. Nevertheless, the following general preparative methods are presented to aid one of skill in the art in synthesizing the inhibitors, with more detailed particular examples being presented in the experimental section describing the working examples.

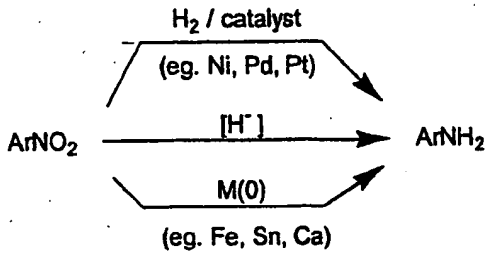
Heterocyclic amines may be synthesized utilizing known methodology (Katritzky, et al. *Comprehensive Heterocyclic Chemistry*; Permagon Press: Oxford, UK (1984). March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985)). For example, 3-substituted-5-aminoisoxazoles (**3**) are available by the reaction of hydroxylamine with an α-cyanoketone (**2**), as shown in Scheme I. Cyanoketone **2**, in turn, is available from the reaction of acetamidate ion with an appropriate acyl derivative, such as an ester, an acid halide, or an acid anhydride. Reaction of an α-cyanoketone with hydrazine (R^2=H) or a monosubstituted hydrazine affords the 3-substituted- or 1,3-disubstituted-5-aminopyrazole (**5**). Pyrazoles unsubstituted at *N*-1 (R^2=H) may be acylated at *N*-1, for example using di-*tert*-butyl dicarbonate, to give pyrazole **7**. Similarly, reaction of nitrile **8** with α-thioacetate ester gives the 5-substituted-3-amino-2-thiophenecarboxylate (**9**, Ishizaki et al. JP 6025221). Decarboxylation of ester **9** may be achieved by protection of the amine, for example as the *tert*-butoxy (BOC) carbamate (**10**), followed by saponification and treatment with acid. When BOC protection is used, decarboxylation may be accompanied by deprotection giving the substituted 3-thiopheneammonium salt **11**. Alternatively, ammonium salt **11** may be directly generated through saponification of ester **9** followed by treatment with acid.



Scheme I. Selected General Methods for Heterocyclic Amine Synthesis

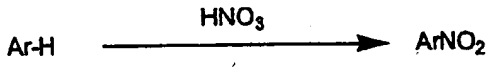
Substituted anilines may be generated using standard methods (March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985). Larock. *Comprehensive Organic Transformations*; VCH Publishers: New York (1989)). As shown in Scheme II, aryl amines are commonly synthesized by reduction of nitroaryls using a metal catalyst, such as Ni, Pd, or Pt, and H_2 or a hydride transfer agent, such as formate, cyclohexadiene, or a borohydride (Rylander. *Hydrogenation Methods*; Academic Press: London, UK (1985)). Nitroaryls may also be directly reduced using a strong hydride source, such as $LiAlH_4$ (Seyden-Penne. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH Publishers: New York (1991)), or using a zero valent metal, such as Fe, Sn or Ca, often in acidic media. Many methods exist

for the synthesis of nitroaryls (March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985). Larock. *Comprehensive Organic Transformations*; VCH Publishers: New York (1989)).

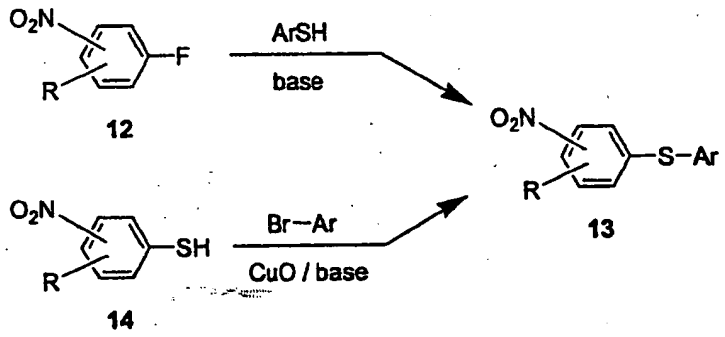


Scheme II Reduction of Nitroaryls to Aryl Amines

Nitroaryls are commonly formed by electrophilic aromatic nitration using HNO_3, or an alternative NO_2^+ source. Nitroaryls may be further elaborated prior to reduction. Thus, nitroaryls substituted with



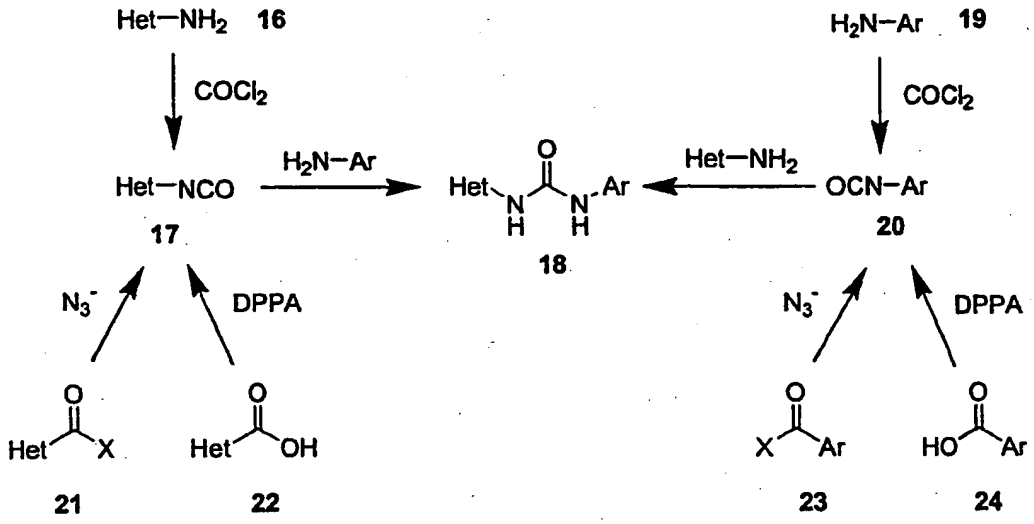
potential leaving groups (eg. F, Cl, Br, etc.) may undergo substitution reactions on treatment with nucleophiles, such as thiolate (exemplified in Scheme III) or phenoxide. Nitroaryls may also undergo Ullman-type coupling reactions (Scheme III).



Scheme III Selected Nucleophilic Aromatic Substitution using Nitroaryls

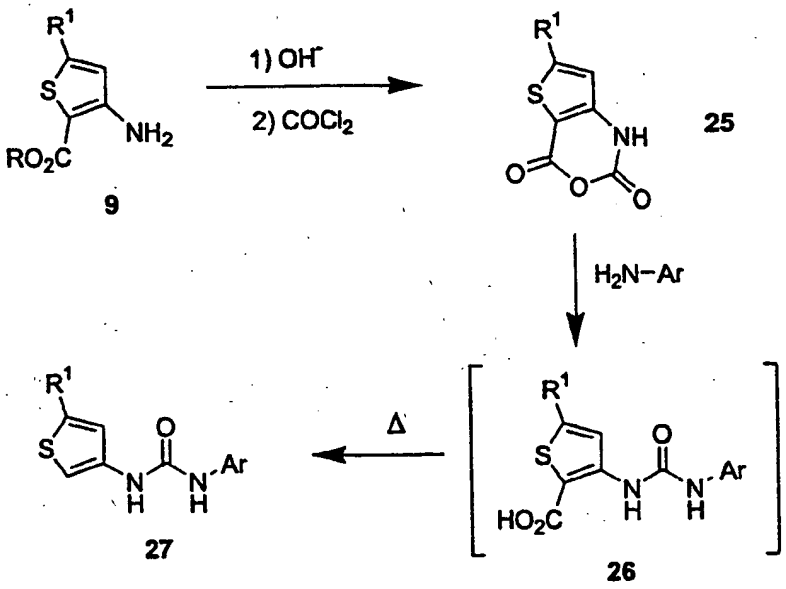
As shown in Scheme IV, urea formation may involve reaction of a heteroaryl isocyanate (17) with an aryl amine (16). The heteroaryl isocyanate may be synthesized from a heteroaryl amine by treatment with phosgene or a phosgene equivalent, such as trichloromethyl chloroformate (diphosgene), bis(trichloromethyl)

carbonate (triphosgene), or *N,N'*-carbonyldiimidazole (CDI). The isocyanate may also be derived from a heterocyclic carboxylic acid derivative, such as an ester, an acid halide or an anhydride by a Curtius-type rearrangement. Thus, reaction of acid derivative **21** with an azide source, followed by rearrangement affords the isocyanate. The corresponding carboxylic acid (**22**) may also be subjected to Curtius-type rearrangements using diphenylphosphoryl azide (DPPA) or a similar reagent. A urea may also be generated from the reaction of an aryl isocyanate (**20**) with a heterocyclic amine.



Scheme IV Selected Methods of Urea Formation (Het = heterocycle)

1-Amino-2-heterocyclic carboxylic esters (exemplified with thiophene **9**, Scheme V) may be converted into an isatoic-like anhydride (**25**) through saponification, followed by treatment with phosgene or a phosgene equivalent. Reaction of anhydride **25** with an aryl amine can generate acid **26** which may spontaneously decarboxylate, or may be isolated. If isolated, decarboxylation of acid **26** may be induced upon heating.



Scheme V Urea Formation via Isatoic-like Anhydrides

Finally, ureas may be further manipulated using methods familiar to those skilled in the art.

The invention also includes pharmaceutical compositions including a compound of this invention as described above, or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier.

The compounds may be administered orally, topically, parenterally, by inhalation or spray, sublingually, or rectally or vaginally in dosage unit formulations. The term 'administration by injection' includes intravenous, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. Dermal administration may include topical application or transdermal administration. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in

order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but

liquid at the rectal or vaginal temperature and will therefore melt in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of the invention may also be administrated transdermally using methods known to those skilled in the art (see, for example: Chien; "Transdermal Controlled Systemic Medications"; Marcel Dekker, Inc.; 1987. Lipp et al. WO94/04157 3Mar94). For example, a solution or suspension of a compound of Formula I in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with additional additives known to those skilled in the art, such as matrix materials and bacteriocides. After sterilization, the resulting mixture can be formulated following known procedures into dosage forms. In addition, on treatment with emulsifying agents and water, a solution or suspension of a compound of Formula I may be formulated into a lotion or salve.

Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include mixtures of one or more materials selected from lower alcohols, lower ketones, lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

Suitable penetration enhancing materials for transdermal delivery system are known to those skilled in the art, and include, for example, monohydroxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated C_8–C_{18} fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated C_8–C_{18} fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl isobutyl tertbutyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristinic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl maleate, or diisopropyl fumarate. Additional

penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbid and diethyleneglycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures of one or more materials selected from monohydroxy or polyhydroxy alcohols, saturated or unsaturated C_8–C_{18} fatty alcohols, saturated or unsaturated C_8–C_{18} fatty acids, saturated or unsaturated fatty esters with up to 24 carbons, diesters of saturated or unsaturated discarboxylic acids with a total of up to 24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers, styrenebutadiene coploymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix components. Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

For all regimens of use disclosed herein for compounds of Formula I, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily inhalation dosage regimen will preferably be from 0.01 to 10 mg/Kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics.

It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy.

It will be further appreciated by one skilled in the art that the optimal course of treatment, ie, the mode of treatment and the daily number of doses of a compound of Formulae I or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatmment tests.

The entire disclosure of all applications, patents and publications cited above and below are hereby incorporated by reference, including provisional application Attorney Docket No. Bayer 11V1, filed December 22, 1997, as SN 08/995,750, and was converted on December 22, 1998.

The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.

EXAMPLES

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon or dry nitrogen, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mmHg.

All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by weight.

Commercial grade reagents and solvents were used without further purification. Thin-layer chromatography (TLC) was performed on Whatman® pre-coated glass-backed silica gel 60A F-254 250 μm plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, (d) immersion of the plate in a cerium sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.

Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier transform intrared spectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; MeOD-d_3; δ 49.0; DMSO-d_6 δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) were obtained with a Hewlett Packard 5989A mass

spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source was maintained at 250 °C. Electron impact ionization was performed with electron energy of 70 eV and a trap current of 300 μA. Liquid-cesium secondary ion mass spectra (FAB-MS), an updated version of fast atom bombardment were obtained using a Kratos Concept 1-H spectrometer. Chemical ionization mass spectra (CI-MS) were obtained using a Hewlett Packard MS-Engine (5989A) with methane as the reagent gas ($1x10^{-4}$ torr to $2.5x10^{-4}$ torr). The direct insertion desorption chemical ionization (DCI) probe (Vaccumetrics, Inc.) was ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra were scanned from 50-800 amu at 2 sec per scan. HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C-18 column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-800 amu using a variable ion time according to the number of ions in the source. Gas chromatography - ion selective mass spectra (GC-MS) were obtained with a Hewlett Packard 5890 gas chromatograph equipped with an HP-1 methyl silicone column (0.33 mM coating; 25 m x 0.2 mm) and a Hewlett Packard 5971 Mass Selective Detector (ionization energy 70 eV).

Elemental analyses were conducted by Robertson Microlit Labs, Madison NJ. All ureas displayed NMR spectra, LRMS and either elemental analysis or HRMS consistant with assigned structures.

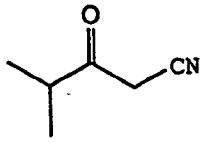
List of Abbreviations and Acronyms:

AcOH	acetic acid
anh	anhydrous
BOC	*tert*-butoxycarbonyl
conc	concentrated
dec	decomposition
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide

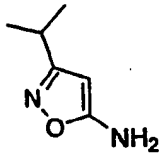
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Et_3N	triethylamine
m-CPBA	3-chloroperoxybenzoic acid
MeOH	methanol
pet. ether	petroleum ether (boiling range 30-60 °C)
THF	tetrahydrofuran
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl

A. General Methods for Synthesis of Hetrocyclic Amines

A2. General Synthesis of 5-Amino-3-alkylisoxazoles

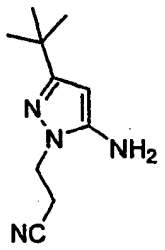


Step 1. 3-Oxo-4-methylpentanenitrile: A slurry of sodium hydride (60% in mineral oil; 10.3 g, 258 mmol) in benzene (52 mL) was warmed to 80 °C for 15 min., then a solution of acetonitrile (13.5 mL, 258 mmol) in benzene (52 mL) was added dropwise *via* addition funnel followed by a solution of ethyl isobutyrate (15 g, 129 mmol) in benzene (52 mL). The reaction mixture was heated overnight, then cooled with an ice water bath and quenched by addition of 2-propanol (50 mL) followed by water (50 mL) *via* addition funnel. The organic layer was separated and set aside. EtOAc (100 mL) was added to the aqueous layer and the resulting mixture was acidified to approximately pH 1 (conc. HCl) with stirring. The resulting aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined with the original organic layer, dried ($MgSO_4$), and concentrated *in vacuo* to give the a-cyanoketone as a yellow oil which was used in the next step without further purification.



Step 2. 5-Amino-3-isopropylisoxazole: Hydroxylamine hydrochloride (10.3 g, 148 mmol) was slowly added to an ice cold solution of NaOH (25.9 g, 645 mmol) in water (73 mL) and the resulting solution was poured into a solution of crude 3-oxo-4-methylpentanenitrile while stirring. The resulting yellow solution was heated at 50 °C for 2.5 hours to produce a less dense yellow oil. The warm reaction mixture was immediately extracted with $CHCl_3$ (3 x 100 mL) without cooling. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oily yellow solid was filtered through a pad of silica (10% acetone/90% CH_2Cl_2) to afford the desired isoxazole as a yellow solid (11.3 g, 70%): mp 63-65 °C; TLC R_f (5% acetone/95% CH_2Cl_2) 0.19; ^{1}H-NMR (DMSO-d_6) d 1.12 (d, *J*=7.0 Hz, 6H), 2.72 (sept, *J*=7.0 Hz, 1H), 4.80 (s, 2H), 6.44 (s, 1H); FAB-MS *m/z* (rel abundance) 127 ($(M+H)^+$; 67%).

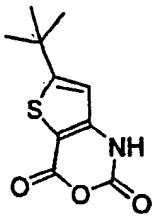
A3. General Method for the Preparation of 5-Amino-1-alkyl-3-alkylpyrazoles



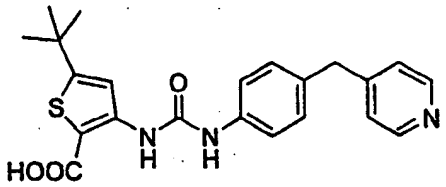
5-Amino-3-tert-butyl-1-(2-cyanoethyl)pyrazole: A solution of 4,4-dimethyl-3-oxopentanenitrile (5.6 g, 44.3 mmol) and 2-cyanoethyl hydrazine (4.61 g, 48.9 mmol) in EtOH (100 mL) was heated at the reflux temperature overnight after which TLC analysis showed incomplete reaction. The mixture was concentrated under reduced pressure and the residue was filtered through a pad of silica (gradient from 40% EtOAc/60% hexane to 70% EtOAc/30% hexane) and the resulting material was triturated (Et_2O/hexane) to afford the desired product (2.5 g, 30%): TLC (30% EtOAc/70% hexane) R_f 0.31; ^{1}H-NMR (DMSO-d_6) δ 1.13 (s, 9H), 2.82 (t, *J*=6.9 Hz, 2H), 4.04 (t, *J*=6.9 Hz, 2H), 5.12 (br s, 2H), 5.13 (s, 1H).

A 4. Synthesis of 3-Amino-5-alkylthiophenes-

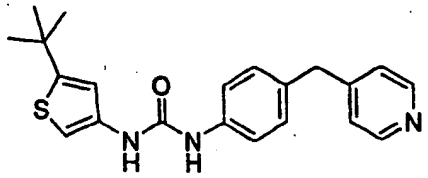
A4a. Synthesis of 3-Amino-5-alkylthiophenes by Thermal Decarboxylation of Thiophenecarboxylic Acids



Step 1. 7-*tert*-Butyl-2H-thieno[3,2-d]oxazine-2,4(1H)-dione: A mixture of methyl 3-amino-5-*tert*-butylthiophenecarboxylate (7.5 g, 35.2 mmol) and KOH (5.92 g) in MeOH (24 mL) and water (24 mL) was stirred at 90 °C for 6 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (600 mL). Phosgene (20% in toluene, 70 mL) was added dropwise over a 2 h period. The resulting mixture was stirred at room temperature overnight and the resulting precipitate was triturated (acetone) to afford the desired anhydride (5.78 g, 73%): ^{1}H-NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.48 (s, 1H), 6.75 (s, 1H); FAB-MS *m/z* (rel abundance) 226 ($(M+H)^+$, 100%).

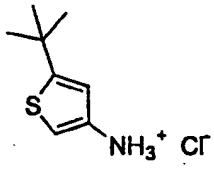


Step 2. *N*-(5-*tert*-Butyl-2-carboxy-3-thienyl)-*N'*-(4-(4-pyridinylmethyl)phenyl)-urea: A solution of 7-*tert*-butyl-2H-thieno[3,2-d]oxazine-2,4(1H)-dione (0.176 g, 0.78 mmol) and 4-(4-pyridinylmethyl)aniline (0.144 g, 0.78 mmol) in THF (5 mL) was heated at the reflux temp. for 25 h. After cooling to room temp., the resulting solid was triturated with Et_2O to afford the desired urea (0.25 g, 78%): mp 187-189 °C; TLC (50% EtOAc/50% pet. ether) R_f 0.04; ^{1}H-NMR (DMSO-d_6) δ 1.34 (s, 9H), 3.90 (s, 2H), 7.15 (d, *J*=7Hz, 2H), 7.20 (d, *J*=3 Hz, 2H), 7.40 (d, *J*=7 Hz, 2H), 7.80 (s 1H), 8.45 (d, *J*=3 Hz, 2H) 9.55 (s, 1H), 9.85 (s, 1H), 12.50 (br s, 1H); FAB-MS *m/z* (rel abundance) 410 ($(M+H)^+$; 20%).



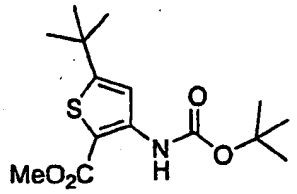
Step 3. ***N*-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-pyridinylmethyl)phenyl)urea:** A vial containing *N*-(5-*tert*-butyl-2-carboxy-3-thienyl)-*N'*-(4-(4-pyridinylmethyl)phenyl)-urea (0.068 g, 0.15 mmol) was heated to 199 °C in an oil bath. After gas evolution ceased, the material was cooled and purified by preparative HPLC (C-18 column; gradient from 20% CH_3CN/79.9% H_2O/0.1% TFA to 99.9% H_2O/0.1% TFA) to give the desired product (0.024 g, 43%): TLC (50% EtOAc/50% pet. ether) R_f 0.18; ^{1}H-NMR (DMSO-d_6) δ 1.33 (s, 9H), 4.12 (s, 2H), 6.77 (s, 1H), 6.95 (s, 1H), 7.17 (d, *J*=9 Hz, 2H), 7.48 (d, *J*=9 Hz, 2H), 7.69 (d, *J*=7 Hz, 1H), 8.58 (s, 1H), 8.68 (d, *J*=7 Hz, 2H), 8.75 (s, 1H); EI-MS *m/z* 365 (M^+).

A4b. Synthesis 3-Amino-5-alkylthiophenes from 3-Amino-5-alkyl-2-thiophene-carboxylate esters

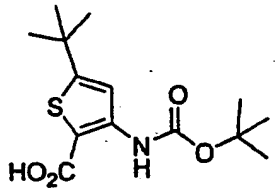


5-*tert*-Butyl-3-thiopheneammonium Chloride: To a solution of methyl 3-amino-5-*tert*-butyl-2-thiophene-carboxylate (5.07 g, 23.8 mmol, 1.0 equiv) in EtOH (150 mL) was added NaOH (2.0 g, 50 mmol, 2.1 equiv). The resulting solution was heated at the reflux temp. for 2.25 h. A conc. HCl solution (approximately 10 mL) was added dropwise with stirring and the evolution of gas was observed. Stirring was continued for 1 h, then the solution was concentrated under reduced pressure. The white residue was suspended in EtOAc (150 mL) and a saturated $NaHCO_3$ solution (150 mL) was added to dissolve. The organic layer was washed with water (150 mL) and a saturated NaCl solution (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give the desired ammonium salt as a yellow oil (3.69 g, 100%). This material was used directly in urea formation without further purification.

A4c. Synthesis 3-Amino-5-alkylthiophenes from *N*-BOC 3-Amino-5-alkyl-2-thiophenecarboxylate esters

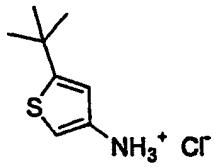


Step 1. Methyl 3-(*tert*-Butoxycarbonylamino)-5-*tert*-butyl-2-thiophenecarboxylate: To a solution of methyl 3-amino-5-*tert*-butyl-2-thiophenecarboxylate (150 g, 0.70 mol) in pyridine (2.8 L) at 5 °C was added di-*tert*-butyl dicarbonate (171.08 g, 0.78 mol, 1.1 equiv) and *N,N*-dimethylaminopyridine (86 g, 0.70 mol, 1.00 equiv) and the resulting mixture was stirred at room temp for 7 d. The resulting dark solution was concentrated under reduced pressure (approximately 0.4 mmHg) at approximately 20 °C. The resulting red solids were dissolved in CH_2Cl_2 (3 L) and sequentially washed with a 1 M H_3PO_4 solution (2 x 750 mL), a saturated $NaHCO_3$ solution (800 mL) and a saturated NaCl solution (2 x 800 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting orange solids were dissolved in abs. EtOH (2 L) by warming to 49 °C, then treated with water (500 mL) to afford the desired product as an off-white solid (163 g, 74%): ^{1}H-NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.51 (s, 9H), 3.84 (s, 3H), 7.68 (s, 1H), 9.35 (br s, 1H); FAB-MS *m/z* (rel abundance) 314 ($(M+H)^+$, 45%).



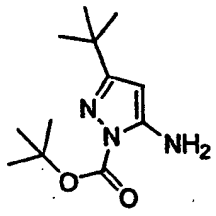
Step 2. 3-(*tert*-Butoxycarbonylamino)-5-*tert*-butyl-2-thiophenecarboxylic Acid: To a solution of methyl 3-(*tert*-butoxycarbonylamino)-5-*tert*-butyl-2-thiophenecarboxylate (90.0 g, 0.287 mol) in THF (630 mL) and MeOH (630 mL) was added a solution of NaOH (42.5 g, 1.06 mL) in water (630 mL). The resulting mixture was heated at 60 °C for 2 h, concentrated to approximately 700 mL under reduced pressure, and cooled to 0 °C. The pH was adjusted to approximately 7 with a 1.0 N HCl solution (approximately 1 L) while maintaining the internal temperature at

approximately 0 °C. The resulting mixture was treated with EtOAc (4 L). The pH was adjusted to approximately 2 with a 1.0 N HCl solution (500 mL). The organic phase was washed with a saturated NaCl solution (4 x 1.5 L), dried (Na_2SO_4), and concentrated to approximately 200 mL under reduced pressure. The residue was treated with hexane (1 L) to form a light pink (41.6 g). Resubmission of the mother liquor to the concentration-precipitation protocol afforded additional product (38.4 g, 93% total yield): ^{1}H-NMR ($CDCl_3$) δ 1.94 (s, 9H), 1.54 (s, 9H), 7.73 (s, 1H), 9.19 (br s, 1H); FAB-MS *m/z* (rel abundance) 300 ($(M+H)^+$, 50%).



Step 3. 5-*tert*-Butyl-3-thiopheneammonium Chloride: A solution of 3-(*tert*-butoxycarbonylamino)-5-*tert*-butyl-2-thiophenecarboxylic acid (3.0 g, 0.010 mol) in dioxane (20 mL) was treated with an HCl solution (4.0 M in dioxane, 12.5 mL, 0.050 mol, 5.0 equiv), and the resulting mixture was heated at 80 °C for 2 h. The resulting cloudy solution was allowed to cool to room temp forming some precipitate. The slurry was diluted with EtOAc (50 mL) and cooled to -20 °C. The resulting solids were collected and dried overnight under reduced pressure to give the desired salt as an off-white solid (1.72 g, 90%): ^{1}H-NMR (DMSO-d_6) δ 1.31 (s, 9H), 6.84 (d, *J*=1.48 Hz, 1H), 7.31 (d, *J*=1.47 Hz, 1H), 10.27 (br s, 3H).

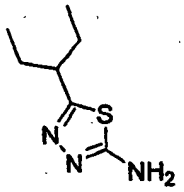
A5. General Method for the Synthesis of BOC-Protected Pyrazoles



5-Amino-3-*tert*-butyl-*N*^{1}-(*tert*-butoxycarbonyl)pyrazole: To a solution of 5-amino-3-*tert*-butylpyrazole (3.93 g, 28.2 mmol) in CH_2Cl_2 (140 mL) was added di-*tert*-butyl dicarbonate (6.22 g, 28.5 mmol) in one portion. The resulting solution was stirred at room temp. for 13 h, then diluted with EtOAc (500 mL). The organic layer was

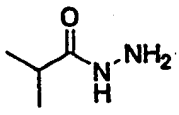
washed with water (2 x 300 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The solid residue was triturated (100 mL hexane) to give the desired carbamate (6.26 g, 92%): mp 63-64 °C; TLC R_f (5% acetone/95% CH_2Cl_2); ^{1}H-NMR (DMSO-d_6) δ 1.15 (s, 9H), 1.54 (s, 9H), 5.22 (s, 1H), 6.11 (s, 2H); FAB-MS *m/z* ($(M+H)^+$).

A6. General Method for the Synthesis of 2-Aminothiadiazoles

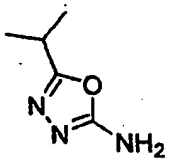


2-Amino-5-(1-(1-ethyl)propyl)thiadiazine: To concentrated sulfuric acid (9.1 mL) was slowly added 2-ethylbutyric acid (10.0 g, 86 mmol, 1.2 equiv). To this mixture was slowly added thiosemicarbazide (6.56 g, 72 mmol, 1 equiv). The reaction mixture was heated at 85 °C for 7 h, then cooled to room temperature, and treated with a concentrated NH_4OHsolution until basic. The resulting solids were filtered to afford 2-amino-5-(1-(1-ethyl)propyl)thiadiazine product was isolated via vacuum filtration as a beige solid (6.3 g, 51%): mp 155-158 °C; TLC (5% MeOH/ 95% $CHCl_3$) R_f 0.14; ^{1}H-NMR (DMSO-d_6) δ 0.80 (t, J=7.35 Hz, 6H), 1.42-1.60 (m, 2H), 1.59-1.71 (m, 2H), 2.65-2.74 (m, 1H), 7.00 (br s, 2H); HPLC ES-MS *m/z* 172 ($(M+H)^+$).

A7. GeneralMethod for the Synthesis of 2-Aminooxadiazoles

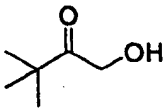


Step 1. Isobutyric Hydrazide: A solution of methyl isobutyrate (10.0 g) and hydrazine (2.76 g) in MeOH (500 mL) was heated at the reflux temperature over night then stirred at 60 °C for 2 weeks. The resulting mixture was cooled to room temperature and concentrated under reduced pressure to afford isobutyric hydrazide as a yellow oil (1.0 g, 10%), which was used inb the next step withour further purification.

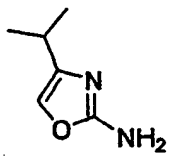


Step 2. 2-Amino-5-isopropyl oxadiazole: To a mixture of isobutyric hydrazide (0.093 g), $KHCO_3$ (0.102 g), and water (1 mL) in dioxane (1 mL) at room temperature was added cyanogen bromide (0.10 g). The resulting mixture was heated at the refulx temperature for 5 h, and stirred at room temperature for 2 d, then treated with CH_2Cl_2 (5 mL). The organic layer was washed with water (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford 2-amino-5-isopropyl oxadiazole as a white solid: HPLC ES-MS *m/z* 128 ($(M+H)^+$).

A8. General Method for the Synthesis of 2-Aminooxazoles



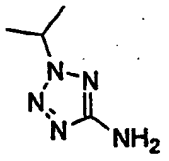
Step 1. 3,3-Dimethyl-1-hydroxy-2-butanone: A neat sample of 1-bromo-3,3-dimethyl-2-butanone (33.3 g) at 0 °C was treated with a 1N NaOH solution, then was stirred for 1 h. The resulting mixture was extracted with EtOAc (5 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure to give 3,3-dimethyl-1-hydroxy-2-butanone (19 g, 100%), which was used inb the next step withour further purification.



Step 2. 2-Amino-4-isopropyl-1,3-oxazole: To a solution of 3,3-dimethyl-1-hydroxy-2-butanone (4.0 g) and cyanimide (50% w/w, 2.86 g) in THF (10 mL) was added a 1N NaOAc solution (8 mL), followed by tetra-*n*-butylammonium hydroxide (0.4 M, 3.6 mL), then a 1N NaOH solution (1.45 mL). The resulting mixtuire was stirred at room temperature for 2 d. The resulting organic layer was separated, washed with water (3 x 25 mL), and the aqueous layer was extraced with Et_2O (3 x 25 mL). The combined organic layers were treated with a 1N NaOH solution tuntil basic, then extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were

dried (Na_2SO_4) and concentrated under reduced pressure to afford 2-Amino-4-isopropyl-1,3-oxazole (1.94 g, 41%): HPLC ES-MS *m/z* 141 ($(M+H)^+$).

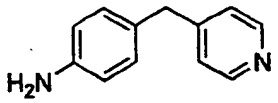
A9. Method for the Synthesis of Substituted-5-aminotetrazoles



: To a solution of 5-aminotetrazole (5 g), NaOH (2.04 g) and water (25 mL) in EtOH (115 mL) at the reflux temperature was added 2-bromopropane (5.9g). The resulting mixture was heated at the reflux temperature for 6 d, then cooled to room temperature, and concentrated under reduced pressure. The resulting aqueous mixture was washed with CH_2Cl_2 (3 x 25 mL), then concentrated under reduced pressure with the aid of a lyophlizer to afford a mixture of 1- and 2-isopropyl-5-aminotetrazole (50%), which was used without further purification: HPLC ES-MS *m/z* 128 ($(M+H)^+$).

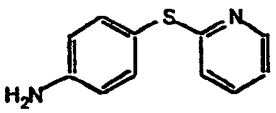
B. General Methods for Synthesis of Substituted Anilines

B1. General Method for Substituted Aniline Formation via Hydrogenation of a Nitroarene



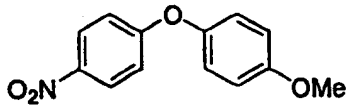
4-(4-Pyridinylmethyl)aniline: To a solution of 4-(4-nitrobenzyl)pyridine (7.0 g, 32.68 mmol) in EtOH (200 mL) was added 10% Pd/C (0.7 g) and the resulting slurry was shaken under a H_2 atmosphere (50 psi) using a Parr shaker. After 1 h, TLC and ^{1}H-NMR of an aliquot indicated complete reaction. The mixture was filtered through a short pad of Celite®. The filtrate was concentrated *in vacuo* to afford a white solid (5.4 g, 90%): ^{1}H-NMR (DMSO-d_6) δ 3.74 (s, 2H), 4.91 (br s, 2H), 6.48 (d, *J*=8.46 Hz, 2H), 6.86 (d, *J*=8.09 Hz, 2H), 7.16 (d, *J*=5.88 Hz, 2H), 8.40 (d, *J*=5.88 Hz, 2H); EI-MS *m/z* 184 (M^+). This material was used in urea formation reactions without further purification.

B2. General Method for Substituted Aniline Formation via Dissolving Metal Reduction of a Nitroarene

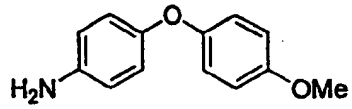


4-(2-Pyridinylthio)aniline: To a solution of 4-(2-pyridinylthio)-1-nitrobenzene (Menai ST 3355A; 0.220 g, 0.95 mmol) and H_2O (0.5 mL) in AcOH (5 mL) was added iron powder (0.317 g, 5.68 mmol) and the resulting slurry stirred for 16 h at room temp. The reaction mixture was diluted with EtOAc (75 mL) and H_2O (50 mL), basified to pH 10 by adding solid K_2CO_3 in portions (***Caution***: foaming). The organic layer was washed with a saturated NaCl solution, dried ($MgSO_4$), concentrated *in vacuo*. The residual solid was purified by MPLC (30% EtOAc/70% hexane) to give the desired product as a thick oil (0.135 g, 70%): TLC (30% EtOAc/70% hexanes) R_f 0.20.

B3a. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

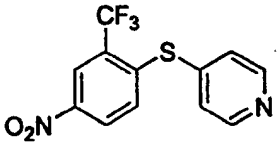


Step 1. 1-Methoxy-4-(4-nitrophenoxy)benzene: To a suspension of NaH (95%, 1.50 g, 59 mmol) in DMF (100 mL) at room temp. was added dropwise a solution of 4-methoxyphenol (7.39 g, 59 mmol) in DMF (50 mL). The reaction was stirred 1 h, then a solution of 1-fluoro-4-nitrobenzene (7.0 g, 49 mmol) in DMF (50 mL) was added dropwise to form a dark green solution. The reaction was heated at 95 °C overnight, then cooled to room temp., quenched with H_2O, and concentrated *in vacuo*. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL) . The organic layer was sequentially washed with H_2O (2 x 200 mL), a saturated $NaHCO_3$ solution (200 mL), and a saturated NaCl solution (200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was triturated (Et_2O/hexane) to afford 1-methoxy-4-(4-nitrophenoxy)benzene (12.2 g, 100%): ^{1}H-NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.93-7.04 (m, 6H), 8.18 (d, *J*=9.2 Hz, 2H); EI-MS *m/z* 245 (M^+).

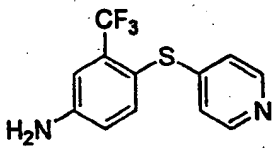


Step 2. 4-(4-Methoxyphenoxy)aniline: To a solution of 1-methoxy-4-(4-nitrophenoxy)benzene (12.0 g, 49 mmol) in EtOAc (250 mL) was added 5% Pt/C (1.5 g) and the resulting slurry was shaken under a H_2 atmosphere (50 psi) for 18 h. The reaction mixture was filtered through a pad of Celite® with the aid of EtOAc and concentrated *in vacuo* to give an oil which slowly solidified (10.6 g, 100%): ^{1}H-NMR ($CDCl_3$) δ 3.54 (br s, 2H), 3.78 (s, 3H), 6.65 (d, *J*=8.8 Hz, 2H), 6.79-6.92 (m, 6H); EI-MS *m/z* 215 (M^+).

B3b. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction



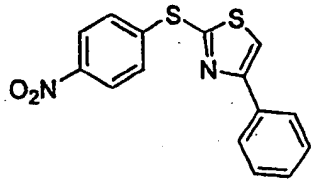
Step 1. 3-(Trifluoromethyl)-4-(4-pyridinylthio)nitrobenzene: A solution of 4-mercaptopyridine (2.8 g, 24 mmoles), 2-fluoro-5-nitrobenzotrifluoride (5 g, 23.5 mmoles), and potassium carbonate (6.1 g, 44.3 mmoles) in anhydrous DMF (80 mL) was stirred at room temperature and under argon overnight. TLC showed complete reaction. The mixture was diluted with Et_2O (100 mL) and water (100 mL) and the aqueous layer was back-extracted with Et_2O (2 x 100 mL). The organic layers were washed with a saturated NaCl solution (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The solid residue was triturated with Et_2O to afford the desired product as a tan solid (3.8 g, 54%): TLC (30% EtOAc/70% hexane) R_f 0.06; ^{1}H-NMR (DMSO-d_6) δ 7.33 (dd, *J*=1.2, 4.2 Hz, 2H), 7.78 (d, *J*=8.7 Hz, 1H), 8.46 (dd, *J*=2.4, 8.7Hz, 1H), 8.54-8.56 (m, 3H).



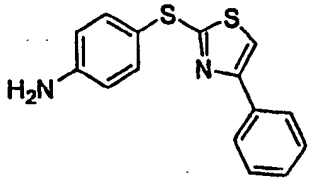
Step 2. 3-(Trifluoromethyl)-4-(4-pyridinylthio)aniline: A slurry of 3-trifluoromethyl-4-(4-pyridinylthio)nitrobenzene (3.8 g, 12.7 mmol), iron powder (4.0 g, 71.6 mmol), acetic acid (100 mL), and water (1 mL) were stirred at room temp. for

4 h. The mixture was diluted with Et_2O (100 mL) and water (100 mL). The aqueous phase was adjusted to pH 4 with a 4 N NaOH solution. The combined organic layers were washed with a saturated NaCl solution (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was filtered through a pad of silica (gradient from 50% EtOAc/50% hexane to 60% EtOAc/40% hexane) to afford the desired product (3.3 g): TLC (50% EtOAc/50% hexane) R_f 0.10; ^{1}H-NMR (DMSO-d_6) δ 6.21 (s, 2H), 6.84-6.87 (m, 3H), 7.10 (d, *J*=2.4 Hz, 1H), 7.39 (d, *J*=8.4 Hz, 1H), 8.29 (d, *J*=6.3 Hz, 2H).

B3c. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

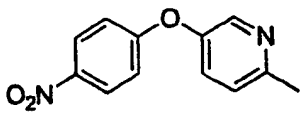


Step 1. 4-(2-(4-Phenyl)thiazolyl)thio-1-nitrobenzene: A solution of 2-mercapto-4-phenylthiazole (4.0 g, 20.7 mmoles) in DMF (40 mL) was treated with 1-fluoro-4-nitrobenzene (2.3 mL, 21.7 mmoles) followed by K_2CO_3 (3.18 g, 23 mmol), and the mixture was heated at approximately 65 °C overnight. The reaction mixture was then diluted with EtOAc (100 mL), sequentially washed with water (100 mL) and a saturated NaCl solution (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The solid residue was triturated with a Et_2O/hexane solution to afford the desired product (6.1 g): TLC (25% EtOAc/75% hexane) R_f 0.49; ^{1}H-NMR ($CDCl_3$) δ 7.35-7.47 (m, 3H), 7.58-7.63 (m, 3H), 7.90 (d, *J*=6.9 Hz, 2H), 8.19 (d, *J*=9.0 Hz, 2H).

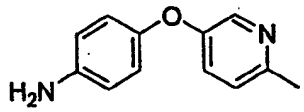


Step 2. 4-(2-(4-Phenyl)thiazolyl)thioaniline: 4-(2-(4-Phenyl)thiazolyl)thio-1-nitrobenzene was reduced in a manner analagous to that used in the preparation of 3-(trifluoromethyl)-4-(4-pyridinylthio)aniline: TLC (25% EtOAc/75% hexane) R_f 0.18; ^{1}H-NMR ($CDCl_3$) δ 3.89 (br s, 2H), 6.72-6.77 (m, 2H), 7.26-7.53 (m, 6H), 7.85-7.89 (m, 2H).

B3d. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

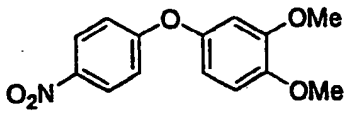


Step 1. 4-(6-Methyl-3-pyridinyloxy)-1-nitrobenzene: To a solution of 5-hydroxy-2-methylpyridine (5.0 g, 45.8 mmol) and 1-fluoro-4-nitrobenzene (6.5 g, 45.8 mmol) in anh DMF (50 mL) was added K_2CO_3 (13.0 g, 91.6 mmol) in one portion. The mixture was heated at the reflux temp. with stirring for 18 h and then allowed to cool to room temp. The resulting mixture was poured into water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organics were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the desired product (8.7 g, 83%). The this material was carried to the next step without further purification.



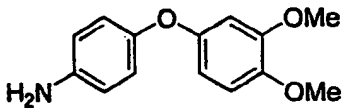
Step 2. 4-(6-Methyl-3-pyridinyloxy)aniline: A solution of 4-(6-methyl-3-pyridinyloxy)-1-nitrobenzene (4.0 g, 17.3 mmol) in EtOAc (150 mL) was added to 10% Pd/C (0.500 g, 0.47 mmol) and the resulting mixture was placed under a H_2 atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was then filtered through a pad of Celite® and concentrated *in vacuo* to afford the desired product as a tan solid (3.2 g, 92%): EI-MS *m/z* 200 (M^+).

B3e. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction



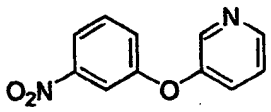
Step 1. 4-(3,4-Dimethoxyphenoxy)-1-nitrobenzene: To a solution of 3,4-dimethoxyphenol (1.0 g, 6.4 mmol) and 1-fluoro-4-nitrobenzene (700 µL, 6.4 mmol) in anh DMF (20 mL) was added K_2CO_3 (1.8 g, 12.9 mmol) in one portion. The mixture was heated at the reflux temp with stirring for 18 h and then allowed to cool to room temp. The mixture was then poured into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were sequentially washed with water (3

x 50 mL) and a saturated NaCl solution (2 x 50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the desired product (0.8 g, 54%). The crude product was carried to the next step without further purification.

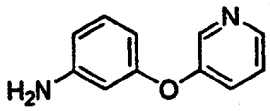


Step 2. **4-(3,4-Dimethoxyphenoxy)aniline**: A solution of 4-(3,4-dimethoxyphenoxy)-1-nitrobenzene (0.8 g, 3.2 mmol) in EtOAc (50 mL) was added to 10% Pd/C (0.100 g) and the resulting mixture was placed under a H_2 atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was then filtered through a pad of Celite® and concentrated *in vacuo* to afford the desired product as a white solid (0.6 g, 75%): EI-MS *m/z* 245 (M^+).

B3f. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction



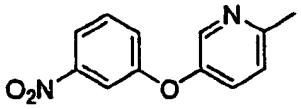
Step 1. **3-(3-Pyridinyloxy)-1-nitrobenzene**: To a solution of 3-hydroxypyridine (2.8 g, 29.0 mmol), 1-bromo-3-nitrobenzene (5.9 g, 29.0 mmol) and copper(I) bromide (5.0 g, 34.8 mmol) in anh DMF (50 mL) was added K_2CO_3 (8.0 g, 58.1 mmol) in one portion. The resulting mixture was heated at the reflux temp. with stirring for 18 h and then allowed to cool to room temp. The mixture was then poured into water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organics were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (30% EtOAc/70% hexane) to afford the desired product (2.0 g, 32 %). This material was used in the next step without further purification.



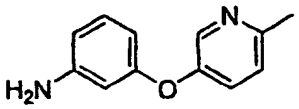
Step 2. **3-(3-Pyridinyloxy)aniline**: A solution of 3-(3-pyridinyloxy)-1-nitrobenzene (2.0 g, 9.2 mmol) in EtOAc (100 mL) was added to 10% Pd/C (0.200 g) and the resulting mixture was placed under a H_2 atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was then filtered through a pad of

Celite® and concentrated *in vacuo* to afford the desired product as a red oil (1.6 g, 94%): EI-MS *m/z* 186 (M^+).

B3g. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

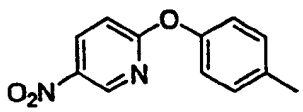


Step 1. 3-(5-Methyl-3-pyridinyloxy)-1-nitrobenzene: To a solution of 3-hydroxy-5-methylpyridine (5.0 g, 45.8 mmol), 1-bromo-3-nitrobenzene (12.0 g, 59.6 mmol) and copper(I) iodide (10.0 g, 73.3 mmol) in anh DMF (50 mL) was added K_2CO_3 (13.0 g, 91.6 mmol) in one portion. The mixture was heated at the reflux temp. with stirring for 18 h and then allowed to cool to room temp. The mixture was then poured into water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organics were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo* . The resulting oil was purified by flash chromatography (30% EtOAc/70% hexane) to afford the desired product (1.2 g, 13%).



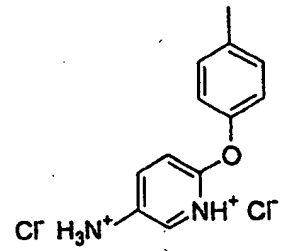
Step 2. 3-(5-Methyl-3-pyridinyloxy)-1-nitrobenzene: A solution of 3-(5-methyl-3-pyridinyloxy)-1-nitrobenzene (1.2 g, 5.2 mmol) in EtOAc (50 mL) was added to 10% Pd/C (0.100 g) and the resulting mixture was placed under a H_2 atmosphere (balloon) and was allowed to stir for 18 h at room temp. The mixture was then filtered through a pad of Celite® and concentrated *in vacuo* to afford the desired product as a red oil (0.9 g, 86%): CI-MS *m/z* 201 ($(M+H)^+$).

B3h. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction



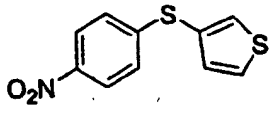
Step 1. 5-Nitro-2-(4-methylphenoxy)pyridine: To a solution of 2-chloro-5-nitropyridine (6.34 g, 40 mmol) in DMF (200 mL) were added of 4-methylphenol (5.4

g, 50 mmol, 1.25 equiv) and K_2CO_3 (8.28 g, 60 mmol, 1.5 equiv). The mixture was stirred overnight at room temp. The resulting mixture was treated with water (600 mL) to generate a precipitate. This mixture was stirred for 1 h, and the solids were separated and sequentially washed with a 1 N NaOH solution (25 mL), water (25 mL) and pet ether (25 mL) to give the desired product (7.05 g, 76%): mp 80-82 °C; TLC (30% EtOAc/70% pet ether) R_f 0.79; ^{1}H-NMR (DMSO-d_6) δ 2.31 (s, 3H), 7.08 (d, *J*=8.46 Hz, 2H), 7.19 (d, *J*=9.20 Hz, 1H), 7.24 (d, *J*=8.09 Hz, 2H), 8.58 (dd, *J*=2.94, 8.82 Hz, 1H), 8.99 (d, *J*=2.95 Hz, 1H); FAB-MS *m/z* (rel abundance) 231 ($(M+H)^+$), 100%).



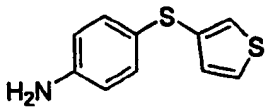
Step 2. 5-Amino-2-(4-methylphenoxy)pyridine Dihydrochloride: A solution 5-nitro-2-(4-methylphenoxy)pyridine (6.94 g, 30 mmol, 1 eq) and EtOH (10 mL) in EtOAc (190 mL) was purged with argon then treated with 10% Pd/C (0.60 g). The reaction mixture was then placed under a H_2 atmosphere and was vigorously stirred for 2.5 h. The reaction mixture was filtered through a pad of Celite®. A solution of HCl in Et_2O was added to the filtrate was added dropwise. The resulting precipitate was separated and washed with EtOAc to give the desired product (7.56 g, 92%): mp 208-210 °C (dec); TLC (50% EtOAc/50% pet ether) R_f 0.42; ^{1}H-NMR (DMSO-d_6) δ 2.25 (s, 3H), 6.98 (d, *J*=8.45 Hz, 2H), 7.04 (d, *J*=8.82 Hz, 1H), 7.19 (d, *J*=8.09 Hz, 2H), 8.46 (dd, *J*=2.57, 8.46 Hz, 1H), 8.63 (d, *J*=2.57 Hz, 1H); EI-MS *m/z* (rel abundance) (M^+, 100%).

B3i. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction



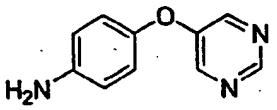
Step 1. 4-(3-Thienylthio)-1-nitrobenzene: To a solution of 4-nitrothiophenol (80%pure; 1.2 g, 6.1 mmol), 3-bromothiophene (1.0 g, 6.1 mmol) and copper(II) oxide (0.5 g, 3.7 mmol) in anhydrous DMF (20 mL) was added KOH (0.3 g, 6.1

mmol), and the resulting mixture was heated at 130 °C with stirring for 42 h and then allowed to cool to room temp. The reaction mixture was then poured into a mixture of ice and a 6N HCl solution (200 mL) and the resulting aqueous mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were sequentially washed with a 1M NaOH solution (2 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo* . The residual oil was purified by MPLC (silica gel; gradient from 10% EtOAc/90% hexane to 5% EtOAc/95% hexane) to afford of the desired product (0.5 g, 34%). GC-MS *m/z* 237 (M^+).



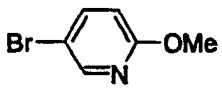
Step 2. 4-(3-Thienylthio)aniline: 4-(3-Thienylthio)-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method B1.

B3j. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction

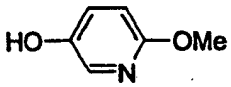


4-(5-Pyrimininyloxy)aniline: 4-Aminophenol (1.0 g, 9.2 mmol) was dissolved in DMF (20 mL) then 5-bromopyrimidine (1.46 g, 9.2 mmol) and K_2CO_3 (1.9 g, 13.7 mmol) were added. The mixture was heated to 100 °C for 18 h and at 130 °C for 48 h at which GC-MS analysis indicated some remaining starting material. The reaction mixture was cooled to room temp. and diluted with water (50 mL). The resulting solution was extracted with EtOAc (100 mL). The organic layer was washed with a saturated NaCl solution (2 x 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residular solids were purified by MPLC (50% EtOAc/50% hexanes) to give the desired amine (0.650 g, 38%).

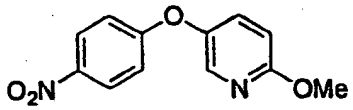
B3k. General Method for Substituted Aniline Formation via Nitroarene Formation Through Nucleophilic Aromatic Substitution, Followed by Reduction



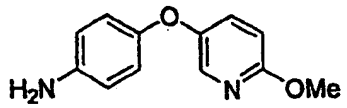
Step 1. 5-Bromo-2-methoxypyridine: A mixture of 2,5-dibromopyridine (5.5 g, 23.2 mmol) and NaOMe (3.76g, 69.6 mmol) in MeOH (60 mL) was heated at 70 °C in a sealed reaction vessel for 42 h, then allowed to cool to room temp. The reaction mixture was treated with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a pale yellow, volatile oil (4.1g, 95% yield): TLC (10% EtOAc / 90% hexane) R_f 0.57.



Step 2. 5-Hydroxy-2-methoxypyridine: To a stirred solution of 5-bromo-2-methoxypyridine (8.9 g, 47.9 mmol) in THF (175 mL) at -78 °C was added an n-butyllithium solution (2.5 M in hexane; 28.7 mL, 71.8 mmol) dropwise and the resulting mixture was allowed to stir at -78 °C for 45 min. Trimethyl borate (7.06 mL, 62.2 mmol) was added via syringe and the resulting mixture was stirred for an additional 2 h. The bright orange reaction mixture was warmed to 0 °C and was treated with a mixture of a 3 N NaOH solution (25 mL, 71.77 mmol) and a hydrogen peroxide solution (30%; approx. 50 mL). The resulting yellow and slightly turbid reaction mixture was warmed to room temp. for 30 min and then heated to the reflux temp. for 1 h. The reaction mixture was then allowed to cool to room temp. The aqueous layer was neutralized with a 1N HCl solution then extracted with Et_2O (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a viscous yellow oil (3.5g, 60%).

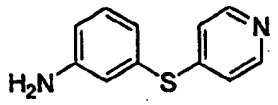


Step 3. 4-(5-(2-Methoxy)pyridyl)oxy-1-nitrobenzene: To a stirred slurry of NaH (97%, 1.0 g, 42 mmol) in anh DMF (100 mL) was added a solution of 5-hydroxy-2-methoxypyridine (3.5g, 28 mmol) in DMF (100 mL). The resulting mixture was allowed to stir at room temp. for 1 h, 4-fluoronitrobenzene (3 mL, 28 mmol) was added via syringe. The reaction mnixture was heated to 95 °C overnight, then treated with water (25 mL) and extracted with EtOAc (2 x 75 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residual brown oil was crystalized EtOAc/hexane) to afford yellow crystals (5.23 g, 75%).



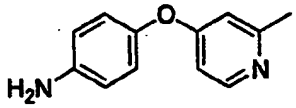
Step 4. **4-(5-(2-Methoxy)pyridyl)oxyaniline:** 4-(5-(2-Methoxy)pyridyl)oxy-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method B3d, Step2.

B4a. General Method for Substituted Aniline Synthesis via Nucleophilic Aromatic Substitution using a Halopyridine



3-(4-Pyridinylthio)aniline: To a solution of 3-aminothiophenol (3.8 mL, 34 mmoles) in anh DMF (90mL) was added 4-chloropyridine hydrochloride (5.4 g, 35.6 mmoles) followed by K_2CO_3 (16.7 g, 121 mmoles). The reaction mixture was stirred at room temp. for 1.5 h, then diluted with EtOAc (100 mL) and water (100mL). The aqueous layer was back-extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with a saturated NaCl solution (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was filtered through a pad of silica (gradient from 50% EtOAc/50% hexane to 70% EtOAc/30% hexane) and the resulting material was triturated with a Et_2O/hexane solution to afford the desired product (4.6 g, 66%): TLC (100 % ethyl acetate) R_f 0.29; ^{1}H-NMR (DMSO-d_6) δ 5.41 (s, 2H), 6.64-6.74 (m, 3H), 7.01 (d, J=4.8, 2H), 7.14 (t, J=7.8 Hz, 1H), 8.32 (d, J=4.8, 2H).

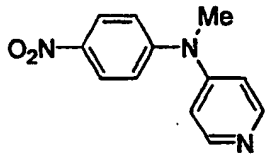
B4b. General Method for Substituted Aniline Synthesis via Nucleophilic Aromatic Substitution using a Halopyridine



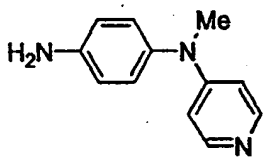
4-(2-Methyl-4-pyridinyloxy)aniline: To a solution of 4-aminophenol (3.6 g, 32.8 mmol) and 4-chloropicoline (5.0 g, 39.3 mmol) in anh DMPU (50 mL) was added potassium *tert*-butoxide (7.4 g, 65.6 mmol) in one portion. The reaction mixture was heated at 100 °C with stirring for 18 h, then was allowed to cool to room temp. The resulting mixture was poured into water (200 mL) and extracted with EtOAc (3 x 150

mL). The combined extracts were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (50 % EtOAc/50% hexane) to afford the desired product as a yellow oil (0.7 g, 9%): CI-MS *m/z* 201 ($(M+H)^+$).

B4c. General Method for Substituted Aniline Synthesis via Nucleophilic Aromatic Substitution using a Halopyridine

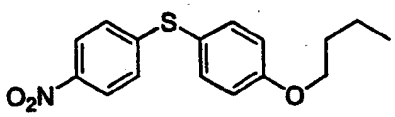


Step 1. Methyl(4-nitrophenyl)-4-pyridylamine: To a suspension of *N*-methyl-4-nitroaniline (2.0 g, 13.2 mmol) and K_2CO_3 (7.2 g, 52.2 mmol) in DMPU (30mL) was added 4-chloropyridine hydrochloride (2.36 g, 15.77 mmol). The reaction mixture was heated at 90 °C for 20 h, then cooled to room temperature. The resulting mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, gradient from 80% EtOAc /20% hexanes to 100% EtOAc) to afford methyl(4-nitrophenyl)-4-pyridylamine (0.42 g)



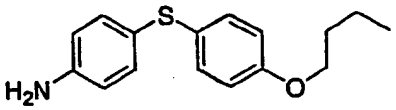
Step 2. Methyl(4-aminophenyl)-4-pyridylamine: Methyl(4-nitrophenyl)-4-pyridylamine was reduced in a manner analogous to that described in Method B1.

B5. General Method of Substituted Aniline Synthesis via Phenol Alkylation Followed by Reduction of a Nitroarene



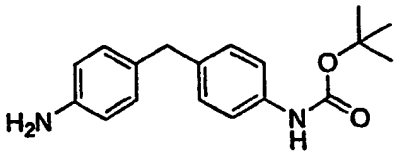
Step 1. 4-(4-Butoxyphenyl)thio-1-nitrobenzene: To a solution of 4-(4-nitrophenyl-thio)phenol (1.50 g, 6.07 mmol) in anh DMF (75 ml) at 0 °C was added NaH (60% in mineral oil, 0.267 g, 6.67 mmol). The brown suspension was stirred at 0 °C until gas

evolution stopped (15 min), then a solution of iodobutane (1.12 g, .690 ml, 6.07 mmol) in anh DMF (20 mL) was added dropwise over 15 min at 0 °C. The reaction was stirred at room temp. for 18 h at which time TLC indicated the presence of unreacted phenol, and additional iodobutane (56 mg, 0.035 mL, 0.303 mmol, 0.05 equiv) and NaH (13 mg, 0.334 mmol) were added. The reaction was stirred an additional 6 h room temp., then was quenched by the addition of water (400 mL). The resulting mixture was extracted with Et_2O (2 x 500 mL). The combibed organics were washed with water (2 x 400 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a clear yellow oil, which was purified by silica gel chromatography (gradient from 20% EtOAc/80% hexane to 50% EtOAc/50% hexane) to give the product as a yellow solid (1.24 g, 67%): TLC (20% EtOAc/80% hexane) R_f 0.75; ^{1}H-NMR (DMSO-d_6) δ 0.92 (t, *J*= 7.5 Hz, 3H), 1.42 (app hex, *J*=7.5 Hz, 2H), 1.70 (m, 2H), 4.01 (t, *J*= 6.6 Hz, 2H), 7.08 (d, *J*=8.7 Hz, 2H), 7.17 (d, *J*=9 Hz, 2H), 7.51 (d, *J*= 8.7 Hz, 2H), 8.09 (d, *J*= 9 Hz, 2H).



Step 2. 4-(4-Butoxyphenyl)thioaniline: 4-(4-Butoxyphenyl)thio-1-nitrobenzene was reduced to the aniline in a manner analagous to that used in the preparation of 3-(trifluoromethyl)-4-(4-pyridinylthio)aniline (Method B3b, Step 2): TLC (33% EtOAc/77% hexane) R_f 0.38.

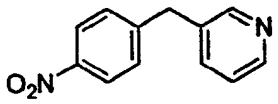
B6. General Method for Synthesis of Substituted Anilines by the Acylation of Diaminoarenes



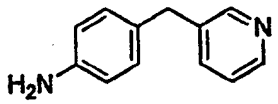
4-(4-*tert*-Butoxycarbamoylbenzyl)aniline: To a solution of 4,4'-methylenedianiline (3.00 g, 15.1 mmol) in anh THF (50 mL) at room temp was added a solution of di-*tert*-butyl dicarbonate (3.30 g, 15.1 mmol) in anh THF (10 mL). The reaction mixture was heated at the reflux temp. for 3 h, at which time TLC indicated the presence of unreacted methylenedianiline. Additional di-*tert*-butyl dicarbonate (0.664 g, 3.03 mmol, 0.02 equiv) was added and the reaction stirred at the reflux temp. for 16 h. The resulting mixture was diluted with Et_2O (200 mL), sequentially washed with a

saturated $NaHCO_3$ solution (100 ml), water (100 mL) and a saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting white solid was purified by silica gel chromatography (gradient from 33% EtOAc/67% hexane to 50% EtOAc/50% hexane) to afford the desired product as a white solid (2.09 g, 46%): TLC (50% EtOAc/50% hexane) R_f 0.45; ^{1}H-NMR (DMSO-d_6) δ 1.43 (s, 9H), 3.63 (s, 2H), 4.85 (br s, 2H), 6.44 (d, *J*=8.4 Hz, 2H), 6.80 (d, *J*=8.1 Hz, 2H), 7.00 (d, *J*=8.4 Hz, 2H), 7.28 (d, *J*=8.1 Hz, 2H), 9.18 (br s, 1H); FAB-MS *m/z* 298 (M^+).

B7. General Method for the Synthesis of Aryl Amines via Electrophilic Nitration Followed by Reduction

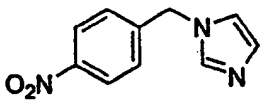


Step 1. 3-(4-Nitrobenzyl)pyridine: A solution of 3-benzylpyridine (4.0 g, 23.6 mmol) and 70% nitric acid (30 mL) was heated overnight at 50 °C. The resulting mixture was allowed to cool to room temp. then poured into ice water (350 mL). The aqueous mixture then made basic with a 1N NaOH solution, then extracted with Et_2O (4 x 100 mL). The combined extracts were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residual oil was purified by MPLC (silica gel; 50 % EtOAc/50% hexane) then recrystallization (EtOAc/hexane) to afford the desired product (1.0 g, 22%): GC-MS *m/z* 214 (M^+).

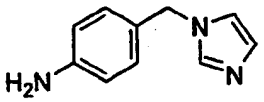


Step 2. 3-(4-Pyridinyl)methylaniline: 3-(4-Nitrobenzyl)pyridine was reduced to the aniline in a manner analogous to that described in Method B1.

B8. General Method for Synthesis of Aryl Amines via Substitution with Nitrobenzyl Halides Followed by Reduction

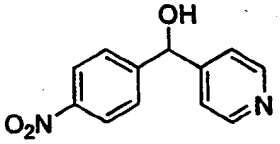


Step 1. 4-(1-Imidazolylmethyl)-1-nitrobenzene: To a solution of imidazole (0.5 g, 7.3 mmol) and 4-nitrobenzyl bromide (1.6 g, 7.3 mmol) in anh acetonitrile (30 mL) was added K_2CO_3 (1.0 g, 7.3 mmol). The resulting mixture was stirred at rooom temp. for 18 h and then poured into water (200 mL) and the resulting aqueous solution wasextracted with EtOAc (3 x 50 mL). The combined organic layers were sequentially washed with water (3 x 50 mL) and a saturated NaCl solution (2 x 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residual oil was purified by MPLC (silica gel; 25% EtOAc/75% hexane) to afford the desired product (1.0 g, 91%): EI-MS *m/z* 203 (M^+).



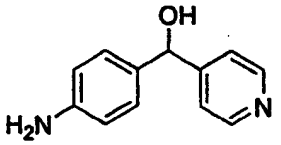
Step 2. 4-(1-Imidazolylmethyl)aniline: 4-(1-Imidazolylmethyl)-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method B2.

B9. Formation of Substituted Hydroxymethylanilines by Oxidation of Nitrobenzyl Compounds Followed by Reduction



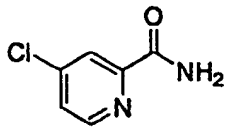
Step 1. 4-(1-Hydroxy-1-(4-pyridyl)methyl-1-nitrobenzene: To a stirred solution of 3-(4-nitrobenzyl)pyridine (6.0 g, 28 mmol) in CH_2Cl_2 (90 mL) was added *m*-CPBA (5.80 g, 33.6 mmol) at 10 °C, and the mixture was stirred at room temp. overnight. The reaction mixture was successively washed with a 10% $NaHSO_3$ solution (50 mL), a saturated K_2CO_3 solution (50 mL) and a saturated NaCl solution (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting yellow solid (2.68 g) was dissolved in anh acetic anhydride (30 mL) and heated at the reflux temperature overnight. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (25 mL) and treated with a 20% aqueous NH_3 solution (30 mL).

The mixture was stirred at room temp. for 1 h, then was concentrated under reduced pressure. The residue was poured into a mixture of water (50 mL) and CH_2Cl_2 (50 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and purified by column chromatography (80% EtOAc/ 20% hexane) to afford the desired product as a white solid. (0.53 g, 8%): mp 110-118 °C; TLC (80% EtOAc/20% hexane) R_f 0.12; FAB-MS *m/z* 367 ($(M+H)^+$, 100%).



Step 2. 4-(1-Hydroxy-1-(4-pyridyl)methylaniline: 4-(1-Hydroxy-1-(4-pyridyl)-methyl-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method B3d, Step2.

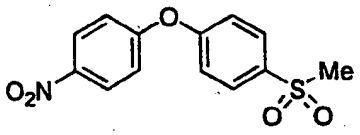
B10. Formation of 2-(*N*-methylcarbamoyl)pyridines via the Menisci reaction



Step 1. 2-(*N*-methylcarbamoyl)-4-chloropyridine. (**Caution**: this is a highly hazardous, potentially explosive reaction.) To a solution of 4-chloropyridine (10.0 g) in *N*-methylformamide (250 mL) under argon at ambient temp was added conc. H_2SO_4 (3.55 mL) (exotherm). To this was added H_2O_2 (17 mL, 30% wt in H2O) followed by $FeSO_4$ 7H2O (0.55 g) to produce an exotherm. The reaction was stirred in the dark at ambient temp for 1h then was heated slowly over 4 h at 45 °C. When bubbling subsided,the reaction was heated at 60 °C for 16 h. The opaque brown solution was diluted with H2O (700 mL) fol.lowed by a 10% NaOH solution (250 mL). The aqueous mixture was extracted with EtOAc (3 x 500 mL) and the organic layers were washed separately with a saturated NaCl solution (3 x 150 mlL. The combined organics were dried ($MgSO_4$) and filtered through a pad of silica gel eluting with EtOAc. The solvent was removed in vacuo and the brown residue was purified by silica gel chromatography (gradient from 50% EtOAc / 50% hexane to 80% EtOAc / 20% hexane). The resulting yellow oil crystallized at 0 °C over 72 h to give 2-(*N*-methylcarbamoyl)-4-chloropyridine in yield (0.61 g, 5.3%): TLC (50% EtOAc/50% hexane) R_f 0.50; MS; ^{1}H NMR ($CDCl_3$): d 8.44 (d, 1 H, J = 5.1 Hz,

CHN), 8.21 (s, 1H, CHCCO), 7.96 (b s, 1H, NH), 7.43 (dd, 1H, J = 2.4, 5.4 Hz, ClCHCN), 3.04 (d, 3H, J = 5.1 Hz, methyl); CI-MS *m/z* 171 ((M+H)+).

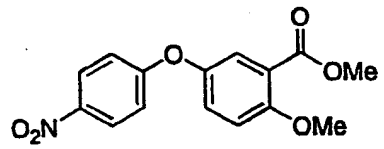
B11. Generalmethod for the Synthesis of ω-Sulfonylphenyl Anilines



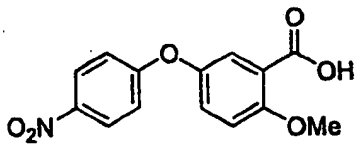
Step 1. 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene: To a solution of 4-(4-methylthiophenoxy)-1-ntirobenzene (2 g, 7.66 mmol) in CH_2Cl_2 (75 mL) at 0 °C was slowly added *m*CPBA (57-86%, 4 g), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was treated with a 1 N NaOH solution (25 mL). The organic layer was sequentially washed with a 1N NaOH solution (25 mL), water (25 mL) and a saturated NaCl solution (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene as a solid (2.1 g).

Step 2. 4-(4-Methylsulfonylphenoxy)-1-aniline: 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene was reduced to the aniline in a manner anaologous to that described in Method B3d, step 2.

B12. General Method for Synthesis of ω-Alkoxy-ω-carboxyphenyl Anilines



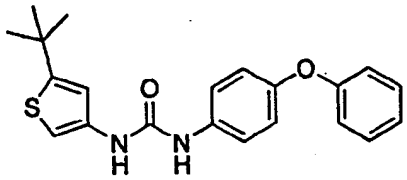
Step 1. 4-(3-Methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene: To a solution of -(3-carboxy-4-hydroxyphenoxy)-1-nitrobenzene (prepared in a manner analogous to that described in Method B3a, step 1, 12 mmol) in acetone (50 mL) was added K_2CO_3 (5 g) and dimethyl sulfate (3.5 mL). The resulting mixture was heated aaaaaat the reflux tempoerature overnight, then cooled to room temperature and filtered through a pad of Celite®. The resulting solution was concentrrated under reduced pressure, absorbed onto silica gel, and purified by column chromatography (50% EtOAc / 50% hexane) to give 4-(3-methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene as a yellow powder (3 g): mp 115.118 °C.



Step 2. 4-(3-Carboxy-4-methoxyphenoxy)-1-nitrobenzene: A mixture of 4-(3-methoxycarbonyl-4-methoxyphenoxy)-1-nitrobenzene (1.2 g), KOH (0.33 g),and water (5 mL) in MeOH (45 mL) was stirred at room temperature overnight and then heated at the reflux temperature for 4 h. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water (50 mL), and the aqueous mixture was made acidic with a 1N HCl solution. The resulting mixture was extracted with EtOAc (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 4-(3-carboxy-4-methoxyphenoxy)-1-nitrobenzene (1.04 g).

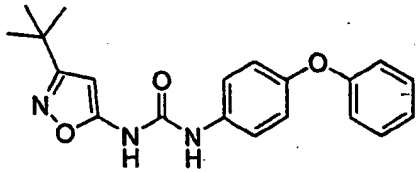
C. General Methods of Urea Formation

C1a. Reaction of a Heterocyclic Amine with an Isocyanate



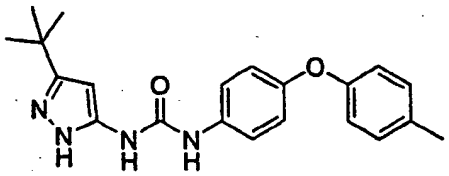
***N*-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-phenoxyphenyl)urea:** To a solution of 5-*tert*-butyl-3-thiophene-ammonium chloride (prepared as described in Method A4b; 7.28 g, 46.9 mmol, 1.0 equiv) in anh DMF (80 mL) was added 4-phenoxyphenyl isocyanate (8.92 g, 42.21 mmol, 0.9 equiv) in one portion. The resulting solution was stirred at 50-60 °C overnight, then diluted with EtOAc (300 mL). The resulting solution was sequentially washed with H_2O (200 mL), a 1 N HCl solution (50 mL) and a saturated NaCl solution (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting off-white solid was recrystallized (EtOAc/hexane) to give a white solid (13.7 g, 88%), which was contaminated with approximately 5% of bis(4-phenoxyphenyl)urea. A portion of this material (4.67 g) was purified by flash chromatography (9% EtOAc/27% CH_2Cl_2/64% cyclohexane) to afforded the desired product as a white solid (3.17 g).

C1b. Reaction of a Heterocyclic Amine with an Isocyanate



***N*-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-phenoxyphenyl)urea**: To a solution of 5-amino-3-*tert*-butylisoxazole (8.93 g, 63.7 mmol, 1 eq.) in CH_2Cl_2 (60 mL) was added 4-phenyloxyphenyl isocyanate (15.47 g, 73.3 mmol, 1.15 eq.) dropwise. The mixture was heated at the reflux temp. for 2 days, eventually adding additional CH_2Cl_2 (80 mL). The resulting mixture was poured into water (500 mL) and extracted with Et_2O (3 x 200 mL). The organic layer was dried ($MgSO_4$) then concentrated under reduced pressure. The residue was recrystallized (EtOAc) to give the desired product (15.7 g, 70%): mp 182-184 °C; TLC (5% acetone/95% acetone) R_f 0.27; ^{1}H-NMR (DMSO-d_6) δ 1.23 (s, 9H), 6.02 (s, 1H), 6.97 (dd, *J*=0.2, 8.8 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 7.08 (t, *J*=7.4 Hz, 1H), 7.34 (m, 2H), 7.45 (dd, *J*=2.2, 6.6 Hz, 2H) , 8.80 (s, 1H), 10.04 (s, 1H); FAB-MS *m/z* (rel abundance) 352 ($(M+H)^+$,70%).

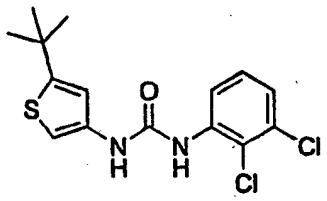
C1c. Reaction of a Heterocyclic Amine with an Isocyanate



***N*-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-methylphenyl)oxyphenyl)urea**: A solution of 5-amino-3-*tert*-butylpyrazole (0.139 g, 1.0 mmol, 1.0 equiv) and 4-(4-methylphenoxy)phenyl isocyanate (0.225 g, 1.0 mmol 1.0 equiv) in toluene (10 mL) was heated at the reflux temp. overnight. The resulting mixture was cooled to room temp and quenched with MeOH (a few mL). After stirring for 30 min, the mixture was concentrated under reduced pressure. The residue was purified by prep. HPLC (silica, 50% EtOAc/50% hexane) to give the desired product (0.121 g, 33%): mp 204 °C; TLC (5% acetone/95% CH_2Cl_2) R_f 0.92; ^{1}H-NMR (DMSO-d_6) δ 1.22 (s, 9H), 2.24 (s, 3H), 5.92 (s, 1H), 6.83 (d, *J*=8.4 Hz, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 7.13 (d,

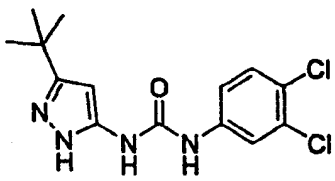
J=8.4 Hz, 2H), 7.40 (d, *J*=8.8 Hz, 2H), 8.85 (s, 1H), 9.20 (br s, 1H), 11.94 (br s, 1H); EI-MS *m/z* 364 (M^+).

C1d. Reaction of a Heterocyclic Amine with an Isocyanate



***N*-(5-*tert*-Butyl-3-thienyl)-*N'*-(2,3-dichlorophenyl)urea**: Pyridine (0.163 mL, 2.02 mmol) was added to a slurry of 5-*tert*-butylthiopheneammonium chloride (Method A4c; 0.30 g, 1.56 mmol) and 2,3-dichlorophenyl isocyanate (0.32 mL, 2.02 mmol) in CH_2Cl_2 (10 mL) to clarify the mixture and the resulting solution was stirred at room temp. overnight. The reaction mixture was then concentrated under reduced pressure and the residue was separated between EtOAc (15 mL) and water (15 mL). The organic layer was sequentially washed with a saturated $NaHCO_3$ solution (15 mL), a 1N HCl solution (15 mL) and a saturated NaCl solution (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. A portion of the residue was by preparative HPLC (C-18 column; 60% acetonitrile/40% water/0.05% TFA) to give the desired urea (0.180 g, 34%): mp 169-170 °C; TLC (20% EtOAc/80% hexane) R_f 0.57; ^{1}H-NMR (DMSO-d_6) δ 1.31 (s, 9H), 6.79 (s, 1H), 7.03 (s, 1H), 7.24-7.33 (m, 2H), 8.16 (dd, *J*=1.84, 7.72 Hz, 1H), 8.35 (s, 1H), 9.60 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 31.9 (3C), 34.0, 103.4, 116.1, 119.3, 120.0, 123.4, 128.1, 131.6, 135.6, 138.1, 151.7, 155.2; FAB-MS *m/z* (rel abundance) 343 ($(M+H)^+$, 83%), 345 ($(M+H+2)^+$, 56%), 347 ($(M+H+4)^+$, 12%).

C1e. Reaction of a Heterocyclic Amine with an Isocyanate

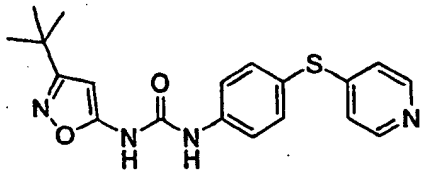


***N*-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(3,4-dichlorophenyl)urea**: A solution of 5-amino-3-*tert*-butyl-*N*^{1}-(*tert*-butoxycarbonyl)pyrazole (Method A5; 0.150 g, 0.63 mmol) and

3,4-dichlorophenyl isocyanate (0.118 g, 0.63 mmol) were in toluene (3.1 mL) was stirred at 55 °C for 2 d. The toluene was removed *in vacuo* and the solid was redissolved in a mixture of CH_2Cl_2 (3 mL) and TFA (1.5 mL). After 30 min, the solvent was removed *in vacuo* and the residue was taken up in EtOAc (10 mL). The resulting mixture was sequentially washed with a saturated $NaHCO_3$ solution (10 mL) and a NaCl solution (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient from 40% EtOAc/ 60% hexane to 55%EtOAc/ 5% hexane) to give the desired product (0.102 g, 48%): mp 182-184 °C; TLC (40% EtOAc/60% hexane) R_f 0.05, FAB-MS *m/z* 327 ($(M+H)^+$).

C2a. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate, then Reaction with Substituted Aniline

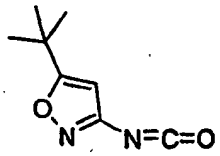
Step 1. 3-*tert*-Butyl-5-isoxazolyl Isocyanate: To a solution of phosgene (20% in toluene, 1.13 mL, 2.18 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added anh. pyridine (0.176 mL, 2.18 mmol), followed by 5-amino-3-*tert*-butylisoxazole (0.305 g, 2.18 mmol). The resulting solution was allowed to warm to room temp. over 1 h, and then was concentrated under reduced pressure. The solid residue dried *in vacuo* for 0.5 h.



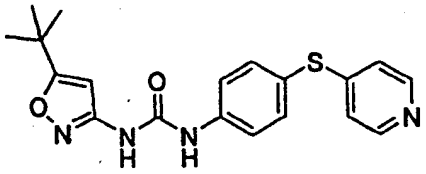
Step 2. *N*-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinylthio)phenyl)urea: The crude 3-*tert*-butyl-5-isoxazolyl isocyanate was suspended in anh toluene (10 mL) and 4-(4-pyridinylthio)aniline (0.200 g, 0.989 mmol) was rapidly added. The suspension was stirred at 80 °C for 2 h then cooled to room temp. and diluted with an EtOAc/CH_2Cl_2 solution (4:1, 125 mL). The organic layer was washed with water (100 mL) and a saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting yellow oil was purified by column chromatography (silica gel, gradient from 2% MeOH/98% CH_2Cl_2 to 4% MeOH/6% CH_2Cl_2) to afford a foam, which was triturated (Et_2O/hexane) in combination with sonication to give the product as a white powder (0.18 g, 49%): TLC (5%

MeOH/95% CH_2Cl_2) R_f 0.21; ^{1}H-NMR (DMSO-d_6) δ 1.23 (s, 9H), 6.06 (s, 1H), 6.95 (d, *J*=5 Hz, 2H), 7.51 (d, *J*=8 Hz, 2H), 7.62 (d, *J*=8 Hz, 2H), 8.32 (d, *J*=5 Hz, 2H), 9.13 (s, 1H), 10 .19 (s, 1H); FAB-MS *m/z* 369 ($(M+H)^+$).

C2b. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate Followed by Reaction with Substituted Aniline



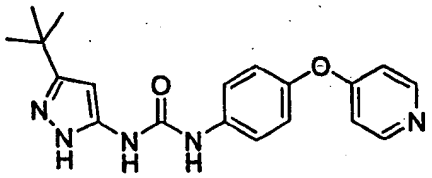
Step 1. 5-*tert*-Butyl-3-isoxazolyl Isocyanate: To a solution of phosgene (148 mL, 1.93 M in toluene, 285 mmol) in anhydrous CH_2Cl_2 (1 L) was added 3-amino-5-*tert*-butylisoxazole (10.0 g, 71 mmol) followed by pyridine (46 mL, 569 mmol). The mixture was allowed to warm to room temp and stirred overnight (ca. 16 h), then mixture was concentrated *in vacuo*. The residue was dissolved in anh. THF (350 mL) and stirred for 10 min. The orange precipitate (pyridinium hydrochloride) was removed and the isocyanate-containing filtrate (approximately 0.2 M in THF) was used as a stock solution: GC-MS (aliquot obtained prior to concentration) *m/z* 166 (M^+).



Step 2. *N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinylthio)phenyl)urea: To a solution of 5-*tert*-butyl-3-isoxazolyl isocyanate (247 mL, 0.2 M in THF, 49.4 mmol) was added 4-(4-pyridinylthio)aniline (5 g, 24.72 mmol), followed by THF (50 mL) then pyridine (4.0 mL, 49 mmol) to neutralize any residual acid. The mixture was stirred overnight (ca. 18 h) at room temp. Then diluted with EtOAc (300 mL). The organic layer was washed successively with a saturated NaCl solution (100 mL), a saturated $NaHCO_3$ solution (100 mL), and a saturated NaCl solution (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting material was purified by MPLC (2 x 300 g silica gel, 30 % EtOAc/70% hexane) to afford the desired product as a white solid (8.24 g, 90 %): mp 178-179 °C; ^{1}H-NMR (DMSO-d_6) δ 1.28 (s, 9H), 6.51

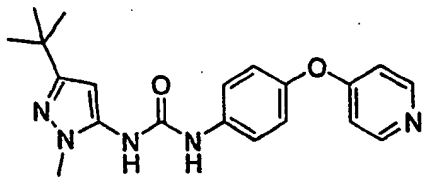
(s, 1H), 6.96 (d, *J*=6.25 Hz, 2H), 7.52 (d, *J*=8.82 Hz, 2H), 7.62 (d, *J*=8.83 Hz, 2H), 8.33 (d, *J*=6.25 Hz, 2H), 9.10 (s, 1H), 9.61 (s, 1H); EI-MS *m/z* 368 (M^+).

C2c. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate Followed by Reaction with Substituted Aniline



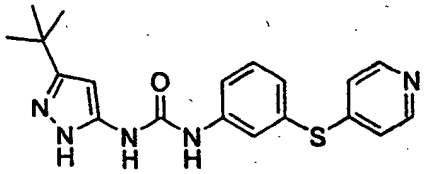
***N*-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyloxy)phenyl)urea**: To a solution of phosgene (1.9M in toluene, 6.8 mL) in anhydrous CH_2Cl_2 (13 mL) at 0 °C was slowly added pyridine (0.105 mL) was added slowly over a 5 min, then 4-(4-pyridinyloxy)aniline (0.250 g, 1.3 mmol) was added in one aliquot causing a transient yellow color to appear. The solution was stirred at 0 °C for 1 h, then was allowed to warm to room temp. over 1 h. The resulting solution was concentrated *in vacuo* then the white solid was suspended in toluene (7 mL). To this slurry, 5-amino-3-*tert*-butyl-*N*^{1}-(*tert*-butoxycarbonyl)pyrazole (0.160 g, 0.67 mmol) was added in one aliquot and the reaction mixture was heated at 70 °C for 12 h forming a white precipitate. The solids were dissolved in a 1N HCl solution and allowed to stir at room temp. for 1 h to form a new precipitate. The white solid was washed (50% Et_2O/50% pet. ether) to afford the desired urea (0.139 g, 59%): mp >228 °C dec; TLC (10% MeOH/ 90% $CHCl_3$) R_f 0.239; ^{1}H-NMR (DMSO-d_6) δ 1.24 (s, 9H), 5.97 (s, 1H), 6.88 (d, *J*=6.25 Hz, 2H), 7.10 (d, *J*=8.82 Hz, 2H), 7.53 (d, *J*=9.2 Hz, 2H), 8.43 (d, *J*=6.25 Hz, 2H), 8.92 (br s, 1H), 9.25 (br s, 1H), 12.00 (br s, 1H); EI-MS *m/z* rel abundance 351 (M^+, 24%).

C3a. Reaction of a Heterocyclic Amine with *N,N'*-Carbonyldiimidazole Followed by Reaction with a Substituted Aniline



***N*-(3-*tert*-Butyl-1-methyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyloxy)phenyl)urea:** To a solution of 5-amino-3-*tert*-butyl-1-methylpyrazole (189 g, 1.24 mol) in anh. CH_2Cl_2 (2.3 L) was added *N,N'*-carbonyldiimidazole (214 g, 1.32 mol) in one portion. The mixture was allowed to stir at ambient temperature for 5 h before adding 4-(4-pyridinyloxy)aniline. The reaction mixture was heated to 36 °C for 16 h. The resulting mixture was cooled to room temp, diluted with EtOAc (2 L) and washed with H_2O (8 L) and a saturated NaCl solution (4 L). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by crystallization (44.4% EtOAc/44.4% Et_2O/11.2% hexane, 2.5 L) to afford the desired urea as a white solid (230 g, 51%): mp 149-152 °C; ^{1}H-NMR (DMSO-d_6) δ 1.18 (s, 9H), 3.57 (s, 3H), 6.02 (s, 1H), 6.85 (d, *J*=6.0 Hz, 2H), 7.08 (d, *J*=9.0 Hz, 2H), 7.52 (d, *J*=9.0 Hz, 2H), 8.40 (d, *J*=6.0 Hz, 2H), 8.46 (s, 1H), 8.97 (s, 1H); FAB-LSIMS *m/z* 366 ($(M+H)^+$).

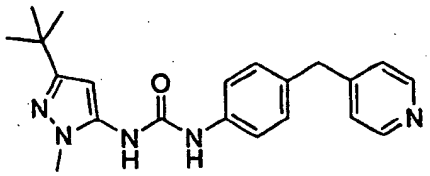
C3b. Reaction of a Heterocyclic Amine with *N,N'*-Carbonyldiimidazole Followed by Reaction with a Substituted Aniline



***N*-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(3-(4-pyridinylthio)phenyl)urea:** To a solution of 5-amino-3-*tert*-butyl-*N*^{1}-(*tert*-butoxycarbonyl)pyrazole (0.282 g, 1.18 mmol) in CH_2Cl_2 (1.2 mL) was added *N,N'*-carbonyldiimidazole (0.200 g, 1.24 mmol) and the mixture was allowed to stir at room temp. for 1 day. 3-(4-Pyridinylthio)aniline (0.239 g, 1.18 mmol) was added to the reaction solution in one aliquot and the resulting mixture was allowed to stir at room temp. for 1 day. Then resulting solution was treated with a 10% citric acid solution (2 mL) and was allowed to stir for 4 h. The organic layer was extracted with EtOAc (3 x 15 mL), dried ($MgSO_4$), and

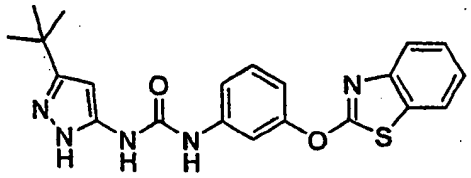
concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (5 mL) and trifluoroacetic acid (2 mL) and the resulting solution was allowed to stir for 4 h. The trifluoroacetic reaction mixture was made basic with a saturated $NaHCO_3$ solution, then extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (5% MeOH/95% CH_2Cl_2). The resulting brown solid was triturated with sonication (50% Et_2O/50% pet. ether) to give the desired urea (0.122 g, 28%): mp >224 °C dec; TLC (5% MeOH/ 95% $CHCl_3$) R_f 0.067; ^{1}H-NMR (DMSO-d_6) δ 1.23 (s, 9H), 5.98 (s, 1H), 7.04 (dm, *J*=13.24 Hz, 2H), 7.15-7.19 (m, 1H), 7.40-7.47 (m, 2H), 7.80-7.82 (m, 1H), 8.36 (dm, *J*=15.44 Hz, 2H), 8.96 (br s, 1H), 9.32 (br s, 1H), 11.97 (br s, 1H); FAB-MS m/z (rel abundance) 368 (M^+, 100%).

C4a. Reaction of Substituted Aniline with *N,N'*-Carbonyldiimidazole Followed by Reaction with a Heterocyclic Amine



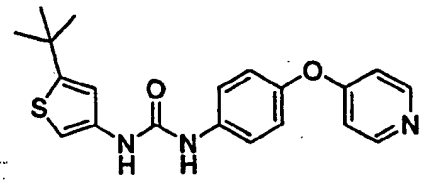
***N*-(3-*tert*-Butyl-1-methyl-5-pyrazolyl)-*N'*-(4-(4-pyridinylmethyl)phenyl)urea**: To a solution of 4-(4-pyridinylmethyl)aniline (0.200 g, 1.08 mmol) in CH_2Cl_2 (10 mL) was added *N,N'*-carbonyldiimidazole (0.200 g, 1.23 mmol). The resulting mixture was stirred at room tempe for 1 h after which TLC analysis indicated no starting aniline. The reaction mixture was then treated with 5-amino-3-*tert*-butyl-1-methylpyrazole (0.165 g, 1.08 mmol) and stirred at 40-45 °C overnight. The reaction mixture was cooled to room temp and purified by column chromatography (gradient from 20% acetone/80% CH_2Cl_2 to 60% acetone/40% CH_2Cl_2) and the resulting solids were crystallized (Et2O) to afford the desired urea (0.227 g, 58%): TLC (4% MeOH/96% CH_2Cl_2) R_f 0.15; ^{1}H-NMR (DMSO-d_6) δ 1.19 (s, 9H), 3.57 (s, 3H), 3.89 (s, 2H), 6.02 (s, 1H), 7.14 (d, *J*=8.4 Hz, 2H), 7.21 (d, *J*=6 Hz, 2H), 7.37 (d, *J*=8.4 Hz, 2H), 8.45-8.42 (m, 3H), 8.81 (s, 1H); FAB-MS *m/z* 364 $(M+H)^+$).

C4b. Reaction of Substituted Aniline with *N,N'*-Carbonyldiimidazole Followed by Reaction with a Heterocyclic Amine



***N*-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(3-(2-benzothiazolyloxy)phenyl)urea**: A solution of 3-(2-benzothiazolyloxy)aniline (0.24 g, 1.0 mmol, 1.0 equiv) and *N.N'*-carbonyldiimidazole (0.162 g, 1.0 mmol, 1.0 equiv) in toluene (10 mL) was stirred at room temp for 1 h. 5-Amino-3-*tert*-butylpyrazole (0.139 g, 1.0 mmol) was added and the resulting mixture was heated at the reflux temp. overnight. The resulting mixture was poured into water and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were concentrated under reduced pressure and dissolved in a minimal amount of CH_2Cl_2. Petroleum ether was added and resulting white precipitate was resubmitted to the crystallization protocol to afford the desired product (0.015 g, 4%): mp 110-111 °C; TLC (5% acetone/95% CH_2Cl_2) R_f 0.05; ^{1}H-NMR (DMSO-d_6) δ 1.24 (s, 9H), 5.97 (s, 1H), 7.00-7.04 (m, 1H), 7.21-7.44 (m, 4H), 7.68 (d, *J*=5.5 Hz, 1H), 7.92 (d, *J*=7.7 Hz, 1H), 7.70 (s, 1H), 8.95 (s, 1H), 9.34 (br s, 1H), 11.98 (br s, 1H); EI-MS *m/z* 408 (M^+).

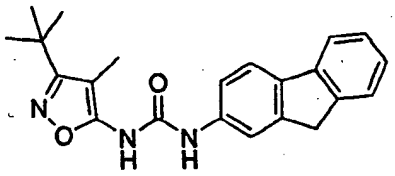
C4c. Reaction of a Heterocyclic Amine with Phosgene to Form an Isocyanate Followed by Reaction with Substituted Aniline



***N*-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-pyridinyloxy)phenyl)urea**: To an ice cold solution phosgene (1.93M in toluene; 0.92 mL, 1.77 mmol) in CH_2Cl_2 (5 mL) was added a solution of 4-(4-pyridinyloxy)aniline (0.30 g, 1.61 mmol) and pyridine (0.255 g, 3.22 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was allowed to warm to room temp. and was stirred for 1 h, then was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL), then treated with 5-*tert*-

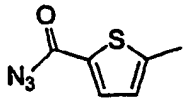
butylthiopheneammonium chloride (Method A4c; 0.206 g, 1.07 mmol), followed by pyridine (0.5 mL). The resulting mixture was stirred at room temp for 1 h, then treated with 2-(dimethylamino)ethylamine (1 mL), followed by stirring at room temp an additional 30 min. The reaction mixture was then diluted with EtOAc (50 mL), sequentially washed with a saturated $NaHCO_3$ solution (50 mL) and a saturated NaCl solution (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 30% EtOAc/70% hexane to 100% EtOAc) to give the desired product (0.38 g , 97%): TLC (50% EtOAc/50% hexane) R_f 0.13; ^{1}H-NMR ($CDCl_3$) δ 1.26 (s, 9H), 6.65 (d, *J*=1.48 Hz, 1H), 6.76 (dd, *J*=1.47, 4.24 Hz, 2H), 6.86 (d, *J*=1.47 Hz, 1H), 6.91 (d, *J*=8.82 Hz, 2H), 7.31 (d, *J*=8.83 Hz, 2H), 8.39 (br s, 2H), 8.41 (d, *J*=1.47 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 32.1 (3C), 34.4, 106.2, 112.0 (2C), 116.6, 121.3 (2C), 121.5 (2C), 134.9, 136.1, 149.0, 151.0 (2C), 154.0, 156.9, 165.2; FAB-MS *m/z* (rel abundance) 368 ($(M+H)^+$, 100%).

C5. General Method for the Reaction of a Substituted Aniline with Triphosgene Followed by Reaction with a Second Substituted Amine

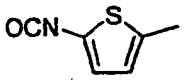


***N*-(3-*tert*-Butyl-4-methyl-5-isoxazolyl)-*N'*-(2-fluorenyl)urea**: To a solution of triphosgene (55 mg, 0.185 mmol, 0.37eq) in 1,2-dichloroethane (1.0mL) was added a solution of 5-amino-4-methyl-3-*tert*-butylisoxazole (77.1 mg, 0.50 mmol, 1.0 eq) and diisopropylethylamine (0.104 mL, 0.60 mmol, 1.2 eq) in 1,2-dichloroethane (1.0 mL). The reaction mixture was stirred at 70 °C for 2 h, cooled to room temp., and treated with a solution of 2-aminofluorene (30.6 mg, 0.50 mmol, 1.0 eq) and diisopropylethylamine (0.087 mL, 1.0 eq) in 1,2-dichloroethane (1.0 mL). The reaction mixture was stirred at 40 °C for 3 h and then at RT for 17 h to produce a precipitate. The solids were washed with Et_2O and hexanes to give the desired urea as a beige solid (25 mg, 14%): mp 179-181 °C; ^{1}H-NMR (DMSO-d_6) δ 1.28 (s, 9H), 2.47 (s, 3H), 3.86 (s, 2H), 7.22 (t, *J*=7.3 Hz, 1H), 7.34 (m, 2H), 7.51 (d, *J*=7.3 Hz, 1H), 7.76 (m, 3H), 8.89 (s, 1H), 9.03 (s, 1H); HPLC ES-MS *m/z* 362 ($(M+H)^+$).

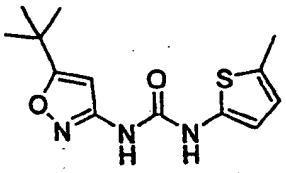
C6. General Method for Urea Formation by Curtius Rearrangement and Carbamate Trapping



Step 1. 5-Methyl-2-(azidocarbonyl)thiophene: To a solution of 5-Methyl-2-thiophenecarboxylic acid (1.06 g, 7.5 mmol) and Et_3N (1.25 mL, 9.0 mmol) in acetone (50 mL) at -10 °C was slowly added ethyl chloroformate (1.07 mL, 11.2 mmol) to keep the internal temperature below 5 °C. A solution of sodium azide (0.83 g, 12.7 mmol) in water (6 mL) was added and the reaction mixture was stirred for 2 h at 0 °C. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated NaCl solution (10 mL). The aqueous layer was back-extracted with CH_2Cl_2 (10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc/ 90% hexanes) to give the azidoester (0.94 g, 75%). Azidoester (100 mg, 0.6 mmol) in anhydrous toluene (10 mL) was heated to reflux for 1 h then cooled to rt. This solution was used as a stock solution for subsequent reactions.



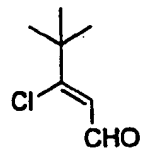
Step 2. 5-Methyl-2-thiophene Isocyanate: 5-Methyl-2-(azidocarbonyl)thiophene (0.100 g, 0.598 mmol) in anh toluene (10 mL) was heated at the reflux temp. for 1 h then cooled to room temp. This solution was used as a stock solution for subsequent reactions.



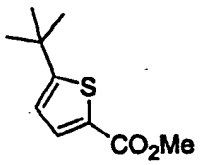
Step 3. *N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(5-methyl-2-thienyl)urea: To a solution of 5-methyl-2-thiophene isocyanate (0.598 mmol) in toluene (10 mL) at room temp. was added 3-amino-5-*tert*-butylisoxazole (0.092 g, 0.658 mmol) and the resulting mixture was stirred overnight. The reaction mixture was diluted with EtOAc (50 mL) and sequentially washed with a 1 N HCl solution (2 x 25 mL) and a saturated NaCl solution (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The

residue was purified by MPLC (20% EtOAc/80% hexane) to give the desired urea (0.156 g, 93%): mp 200-201 °C; TLC (20% EtOAc/80% hexane) R_f 0.20; EI-MS *m/z* 368 (M^+).

C7. General Methods for Urea Formation by Curtius Rearrangement and Isocyanate Trapping

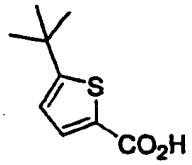


Step 1. 3-Chloro-4,4-dimethylpent-2-enal: $POCl_3$ (67.2 mL, 0.72 mol) was added to cooled (0 °C) DMF (60.6 mL, 0.78 mol) at rate to keep the internal temperature below 20 °C. The viscous slurry was heated until solids melted (approximately 40 °C), then pinacolone (37.5 mL, 0.30 mol) was added in one portion. The reaction mixture was then to 55 °C for 2h and to 75 °C for an additional 2 h. The resulting mixture was allowed to cool to room temp., then was treated with THF (200 mL) and water (200 mL), stirred vigorously for 3 h, and extracted with EtOAc (500 mL). The organic layer was washed with a saturated NaCl solution (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was filtered through a pad of silica (CH_2Cl_2) to give the desired aldehyde as an orange oil (15.5 g, 35%): TLC (5% EtOAc/95% hexane) R_f 0.54; ^{1}H NMR ($CDCl_3$) d 1.26 (s, 9H), 6.15 (d, *J*=7.0 Hz, 1H), 10.05 (d, *J*=6.6 Hz, 1H).

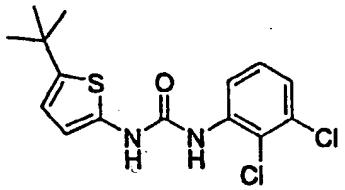


Step 2. Methyl 5-*tert*-butyl-2-thiophenecarboxylate: To a solution of 3-chloro-4,4-dimethylpent-2-enal (1.93 g, 13.2 mmol) in anh. DMF (60 mL) was added a solution of Na_2S (1.23 g, 15.8 mmol) in water (10 mL). The resulting mixture was stirred at room temp. for 15 min to generate a white precipitate, then the slurry was treated with methyl bromoacetate (2.42 g, 15.8 mmol) to slowly dissolve the solids. The reaction mixture was stirred at room temp. for 1.5 h, then treated with a 1 N HCl solution (200 mL) and stirred for 1 h. The resulting solution was extracted with EtOAc (300 mL). The organic phase was sequentially washed with a 1 N HCl solution (200 mL), water (2 x 200 mL) and a saturated NaCl solution (200 mL), dried

(Na_2SO_4) and concentrated under reduced pressure. The residue was purified using column chromatography (5% EtOAc/95% hexane) to afford the desired product (0.95 g, 36%): TLC (20% EtOAc/80% hexane) R_f 0.79; ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H), 3.85 (s, 3H), 6.84 (d, *J*=3.7 Hz, 1H), 7.62 (d, *J*=4.1 Hz, 1H); GC-MS *m/z* (rel abundance) 198 (M^+, 25%).



Step 3. 5-*tert*-Butyl-2-thiophenecarboxylic acid: Methyl 5-*tert*-butyl-2-thiophenecarboxylate (0.10 g, 0.51 mmol) was added to a KOH solution (0.33 M in 90% MeOH/10% water, 2.4 mL, 0.80 mmol) and the resulting mixture was heated at the reflux temperature for 3 h. EtOAc (5 mL) was added to the reaction mixture, then the pH was adjusted to approximately 3 using a 1 N HCl solution. The resulting organic phase was washed with water (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure (0.4 mmHg) to give the desired carboxylic acid as a yellow solid (0.067 g, 73%): TLC (20% EtOAc/79.5% hexane/0.5% AcOH) R*f* 0.29; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 6.89 (d, *J*=3.7 Hz, 1H), 7.73 (d, *J*=3.7 Hz, 1H), 12.30 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.1 (3C), 35.2, 122.9, 129.2, 135.1, 167.5, 168.2.



Step 4. *N*-(5-*tert*-Butyl-2-thienyl)-*N'*-(2,3-dichlorophenyl)urea: A mixture of 5-*tert*-butyl-2-thiophenecarboxylic acid (0.066 g, 0.036 mmol), DPPA (0.109 g, 0.39 mmol) and Et_3N (0.040 g, 0.39 mmol) in toluene (4 mL) was heated to 80 °C for 2 h, 2,3-dichloroaniline (0.116 g, 0.72 mmol) was added, and the reaction mixture was heated to 80°C for an additional 2 h. The resulting mixture was allowed to cool to room temp. and treated with EtOAc (50 mL). The organic layer was washed with a 1 N HCl solution (3 x 50 mL), a saturated $NaHCO_3$ solution (50 mL), and a saturated NaCl solution (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/95% hexane) to afford the desired urea as a purple solid (0.030 g, 24%): TLC (10% EtOAc/90% hexane) R*f* 0.28; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9H), 6.59 (br s, 2H), 7.10-7.13 (m, 2H),

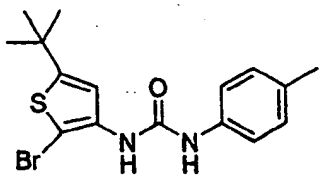
7.66 (br s, 1H), 8.13 (dd, *J*=2.9, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 32.2 (3C), 34.6, 117.4, 119.0[7], 119.1[5], 119.2, 121.5, 124.4, 127.6, 132.6, 135.2, 136.6, 153.4; HPLC ES-MS *m/z* (rel abundance) 343 ($(M+H)^+$, 100%), 345 ($(M+H+2)^+$, 67%), 347 ($(M+H+4)^+$, 14%).

C8. Combinatorial Method for the Synthesis of Diphenyl Ureas Using Triphosgene

One of the anilines to be coupled was dissolved in dichloroethane (0.10 M). This solution was added to a 8 mL vial (0.5 mL) containing dichloroethane (1 mL). To this was added a triphosgene solution (0.12 M in dichloroethane, 0.2 mL, 0.4 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.). The vial was capped and heat at 80 °C for 5 h, then allowed to cool to room temp for approximately 10 h. The second aniline was added (0.10 M in dichloroethane, 0.5 mL, 1.0 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.). The resulting mixture was heated at 80 °C for 4 h, cooled to room temperature and treated with MeOH (0.5 mL). The resulting mixture was concentrated under reduced pressure and the products were purified by reverse phase HPLC.

D. Misc. Methods of Urea Synthesis

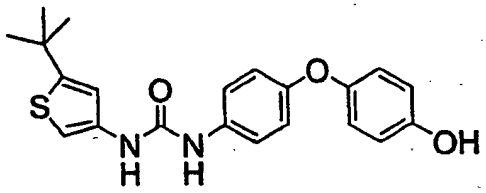
D1. Electrophylic Halogenation



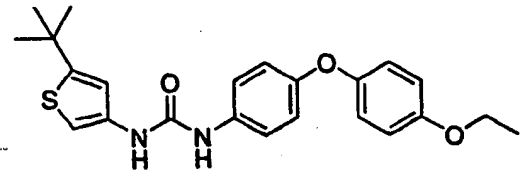
***N*-(2-Bromo-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea**: To a slurry of *N*-(5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea (0.50 g, 1.7 mmol) in $CHCl_3$ (20 mL) at room temp was slowly added a solution of Br_2 (0.09 mL, 1.7 mmol) in $CHCl_3$ (10 mL) via addition funnel causing the reaction mixture to become homogeneous. Stirring was continued 20 min after which TLC analysis indicated complete reaction. The reaction was concentrated under reduced pressure, and the residue triturated (2 x Et_2O/hexane) to give the brominated product as a tan powder (0.43 g, 76%): mp 161-163 °C; TLC (20% EtOAc/ 80% hexane) R_f 0.71; ^1H NMR (DMSO-d_6) δ 1.29 (s, 9H), 2.22 (s, 3H), 7.07 (d, *J*=8.46 Hz, 2H), 7.31 (d, *J*=8.46 Hz, 2H), 7.38 (s, 1H), 8.19

(s, 1H), 9.02 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.3, 31.6 (3C), 34.7, 89.6, 117.5, 118.1 (2C), 129.2 (2C), 130.8, 136.0, 136.9, 151.8, 155.2; FAB-MS *m/z* (rel abundance) 367 ($(M+H)^+$, 98%), 369 $(M+2+H)^+$, 100%).

D2. Synthesis of ω-Alkoxy Ureas



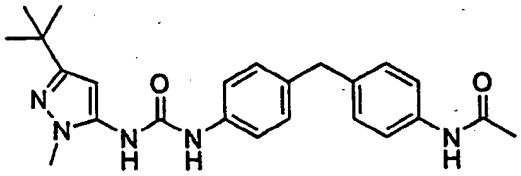
Step 1. ***N*-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl)urea:** A solution of *N*-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-methoxyphenyl)oxyphenyl)urea (1.2 g, 3 mmol) in CH_2Cl_2 (50 mL) was cooled to -78 °C and treated with BBr_3 (1.0 M in CH_2Cl_2, 4.5 mL, 4.5 mmol, 1.5 equiv) dropwise via syringe. The resulting bright yellow mixture was warmed slowly to room temp and stirred overnight. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), then washed with a saturated $NaHCO_3$ solution (50 mL) and a saturated NaCl solution (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified via flash chromatography (gradient from 10% EtOAc/90% hexane to 25% EtOAc/75% hexane) to give the desired phenol as a tan foam (1.1 g, 92%): TLC (20% EtOAc/80% hexane) R_f 0.23; ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 9H), 6.72-6.84 (m, 7H), 6.97 (d, *J*=1.47 Hz, 1H), 7.37 (dm, *J*=9.19 Hz, 2H), 8.49 (s, 1H), 8.69 (s, 1H), 9.25 (s, 1H); FAB-MS *m/z* (rel abundance) 383 ($(M+H)^+$, 33%).



Step 2. ***N*-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-ethoxyphenyl)oxyphenyl)urea:** To a mixture of *N*-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl)urea (0.20 g, 0.5 mmol) and Cs_2CO_3 (0.18 g, 0.55 mmol, 1.1 equiv) in reagent grade acetone (10 mL) was added ethyl iodide (0.08 mL, 1.0 mmol, 2 equiv) via syringe, and the resulting slurry was heated at the reflux temp. for 17 h. The reaction was cooled, filtered, and the solids were washed with EtOAc. The combined organics were concentrated under reduced pressure, and the residue was purified via preparative

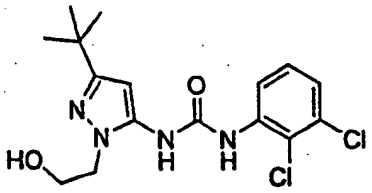
HPLC (60% CH_3CN/40% H_2O/0.05% TFA) to give the desired urea as a colorless powder (0.16 g, 73%): mp 155-156 °C; TLC (20% EtOAC/ 80% hexane) R_f 0.40; ^{1}H-NMR (DMSO-d_6) δ 1.30 (s, 9H), 1.30 (t, *J*=6.99 Hz, 3H), 3.97 (q, *J*=6.99 Hz, 2H), 6.80 (d, *J*=1.47 Hz, 1H), 6.86 (dm, *J*=8.82 Hz, 2H), 6.90 (s, 4H), 6.98 (d, *J*=1.47, 1H), 7.40 (dm, *J*=8.83 Hz, 2H), 8.54 (s, 1H), 8.73 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 14.7, 32.0 (3C), 33.9, 63.3, 102.5, 115.5 (2C), 116.3, 118.4 (2C), 119.7 (2C), 119.8 (2C), 135.0, 136.3, 150.4, 152.1, 152.4, 154.4, 154.7; FAB-MS *m/z* (rel abundance) 411 ($(M+H)^+$, 15%).

D3. Synthesis of ω-Carbamoyl Ureas



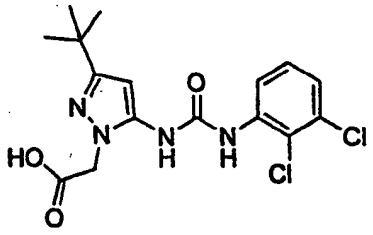
***N*-(3-*tert*-Butyl-1-methyl-5-pyrazolyl)-*N'*-(4-(4-acetaminophenyl)methylphenyl)urea**: To a solution of *N*-(3-*tert*-butyl-1-methyl-5-pyrazolyl)-*N'*-(4-(4-aminophenyl)methylphenyl)urea (0.300 g, 0.795 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added acetyl chloride (0.057 mL, 0.795 mmol), followed by anhydrous Et_3N (0.111 mL, 0.795 mmol). The solution was allowed to warm to room temp over 4 h, then was diluted with EtOAc (200 mL). The organic layer was sequentially washed with a 1M HCl solution (125 mL) then water (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was purified by filtration through a pad of silica (EtOAc) to give the desired product as a white solid (0.160 g, 48%): TLC (EtOAc) R_f 0.33; ^{1}H-NMR (DMSO-d_6) δ 1.17 (s, 9H), 1.98 (s, 3H), 3.55 (s, 3H), 3.78 (s, 2H), 6.00 (s, 1H), 7.07 (d, *J*=8.5 Hz, 2H), 7.09 (d, *J*=8.5 Hz, 2H), 7.32 (d, *J*=8.5 Hz, 2H), 7.44 (d, *J*=8.5 Hz, 2H), 8.38 (s, 1H), 8.75 (s, 1H), 9.82 (s, 1H); FAB-MS *m/z* 420 ($(M+H)^+$).

D4. General Method for the Conversion of Ester-Containing Ureas into Alcohol-Containing Ureas



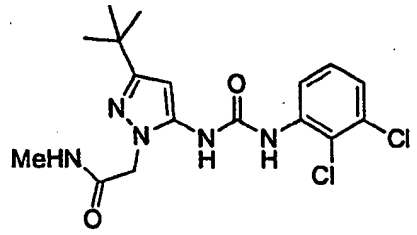
N-(*N*^{1}-(2-Hydroxyethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea: A solution of *N*-(*N*^{1}-(2-(2,3-dichlorophenylamino)carbonyloxyethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea (prepared as described in Method A3; 0.4 g, 0.72 mmoles) and NaOH (0.8 mL, 5N in water, 4.0 mmoles) in EtOH (7 mL) was heated at ~65 °C for 3 h at which time TLC indicated complete reaction. The reaction mixture was diluted with EtOAc (25 mL) and acidified with a 2N HCl solution (3 mL). The resulting organic phase was washed with a saturated NaCl solution (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was crystallized (Et_2O) to afford the desired product as a white solid (0.17 g, 64 %): TLC (60% EtOAc/40% hexane) R_f 0.16; ^{1}H-NMR (DMSO-d_6) δ 1.23 (s, 9H), 3.70 (t, *J*=5.7 Hz, 2H), 4.10 (t, *J*=5.7 Hz, 2H), 6.23 (s, 1H), 7.29-7.32 (m, 2H), 8.06-8.09 (m, 1H), 9.00 (br s, 1H), 9.70 (br s, 1H); FAB-MS *m/z* (rel abundance) 371 ($(M+H)^+$, 100%).

D5a. General Method for the Conversion of Ester-Containing Ureas into Amide-Containing Ureas



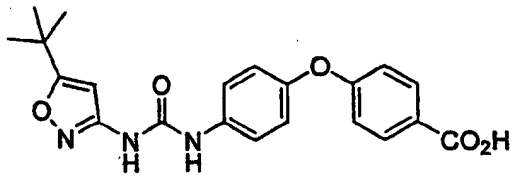
Step 1. ***N*-(*N*^{1}-(Carboxymethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea**: A solution of *N*-(*N*^{1}-(ethoxycarbonylmethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea (prepared as described in Method A3, 0.46 g, 1.11 mmoles) and NaOH (1.2 mL, 5N in water, 6.0 mmoles) in EtOH (7 mL) was stirred at room temp. for 2 h at which time TLC indicated complete reaction. The reaction mixture was diluted with EtOAc (25 mL) and acidified with a 2N HCl

solution (4 mL). The resulting organic phase was washed with a saturated NaCl solution (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was crystallized (Et_2O/hexane) to afford the desired product as a white solid (0.38 g, 89%): TLC (10% MeOH/90% CH_2Cl_2) R_f 0.04; ^{1}H-NMR (DMSO-d_6) δ 1.21 (s, 9H), 4.81 (s, 2H), 6.19 (s, 1H), 7.28-7.35 (m, 2H), 8.09-8.12 (m, 1H), 8.76 (br s, 1H), 9.52 (br s, 1H); FAB-MS *m/z* (rel abundance) 385 ($(M+H)^+$, 100%).

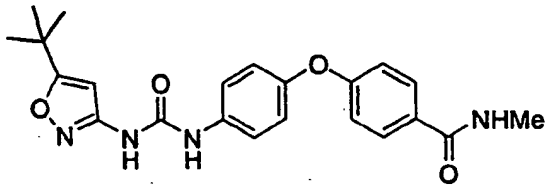


Step 2. ***N*-(*N*^{1}-((Methylcarbamoyl)methyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea:** A solution of *N*-(*N*^{1}-(carboxymethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea (100 mg, 0.26 mmole) and *N,N'*-carbonyldiimidazole (45 mg, 0.28 mmole) in CH_2Cl_2 (10 mL) was stirred at room temp. 4 h at which time TLC indicated formation of the corresponding anhydride (TLC (50% acetone/50% CH_2Cl_2) R_f 0.81). Dry methylamine hydrochloride (28 mg, 0.41 mmole) was then added followed by of diisopropylethylamine (0.07 mL, 0.40 mmole). The reaction mixture was stirred at room temp. overnight, then diluted with CH_2Cl_2, washed with water (30 mL), a saturated NaCl solution (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 10% acetone/90% CH_2Cl_2 to 40% acetone/60% CH_2Cl_2) and the residue was crystallized (Et_2O/hexane) to afford the desired product (47 mg, 46%): TLC (60% acetone/40% CH_2Cl_2) R_f 0.59; ^{1}H-NMR (DMSO-d_6) δ 1.20 (s, 9H), 2.63 (d, *J*=4.5 Hz, 3H), 4.59 (s, 2H), 6.15 (s, 1H), 7.28-7.34 (m, 2H), 8.02-8.12 (m, 2H), 8.79 (br s, 1H), 9.20 (br s, 1H); FAB-MS *m/z* (rel abundance) 398 ($(M+H)^+$, 30%).

D5b. General Method for the Conversion of Ester-Containing Ureas into Amide-Containing Ureas

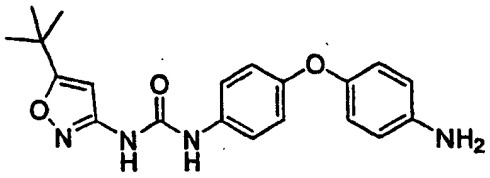


Step 1. ***N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-carboxyphenyl)oxyphenyl)urea:** To a solution of *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-ethoxyoxycarbonylphenyl)-oxyphenyl)urea (0.524 g, 1.24 mmol) in a mixture of EtOH (4 mL) and THF (4 mL) was added a 1M NaOH solution (2 mL) and the resulting solution was allowed to stir overnight at room temp. The resulting mixture was diluted with water (20 mL) and treated with a 3M HCl solution (20 mL) to form a white precipitate. The solids were washed with water (50 mL) and hexane (50 mL) , and then dried (approximately 0.4 mmHg) to afford the desired product (0.368 g, 75 %). This material was carried to the next step without further purification.



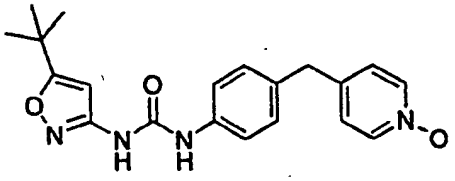
Step 2. ***N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-(*N*-methylcarbamoyl)-phenyl)oxyphenyl)urea:** A solution of *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-carboxyphenyl)oxyphenyl)urea (0.100 g, 0.25 mmol), methylamine (2.0 M in THF; 0.140 mL, 0.278 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (76 mg, 0.39 mmol), and *N*-methylmorpholine (0.030 mL, 0.27 mmol) in a mixture of THF (3 mL) and DMF (3mL) was allowed to stir overnight at room temp. then was poured into a 1M citric acid solution (20 mL) and extracted with EtOAc (3 x 15 mL). The combined extracts were sequentially washed with water (3 x 10 mL) and a saturated NaCl solution (2 x 10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* . The resulting crude oil was purified by flash chromatography (60 % EtOAc/40% hexane) to afford the desired product as a white solid (42 mg, 40%): EI-MS *m/z* 409 ($(M+H)^+$).

D6. General Method for the Conversion of ω-Amine-Containing Ureas into Amide-Containing Ureas



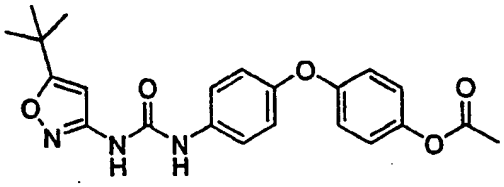
***N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-aminophenyl)oxyphenyl)urea:** To a solution of *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-*tert*-butoxycarbonylaminophenyl)oxyphenyl)-urea (prepared in a manner analogous to Methods B6 then C2b; 0.050 g, 0.11 mmol) in anh 1,4-dioxane (3 mL) was added a conc HCl solution (1 mL) in one portion and the mixture was allowed to stir overnight at room temp . The mixture was then poured into water (10 mL) and EtOAc(10 mL) and made basic using a 1M NaOH solution (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were sequentially washed with water (3 x 100 mL) and a saturated NaCl solution (2 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the desired product as a white solid (26 mg, 66%). EI-MS *m/z* 367 ($(M+H)^+$).

D7. General Method for the Oxidation of Pyridine-Containing Ureas



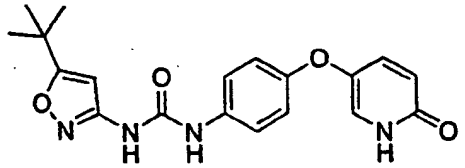
***N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(*N*-oxo-4-pyridinyl)methylphenyl)urea:** To a solution of *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea (0.100 g, 0.29 mmol) in $CHCl_3$ (10 mL) was added *m*-CPBA (70% pure, 0.155 g, 0.63 mmol) and the resulting solution was stirred at room temp for 16 h. The reaction mixture was then treated with a saturated K_2CO_3 solution (10 mL). After 5 min, the solution was diluted with $CHCl_3$ (50 mL). The organic layer was washed successively with a saturated aqueous $NaHSO_3$ solution (25 mL), a saturated $NaHCO_3$ solution (25 mL) and a saturated NaCl solution (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residual solid was purified by MPLC (15% MeOH/85% EtOAc) to give the *N*-oxide (0.082 g, 79%).

D8. General Method for the Acylation of a Hydroxy-Containing Urea

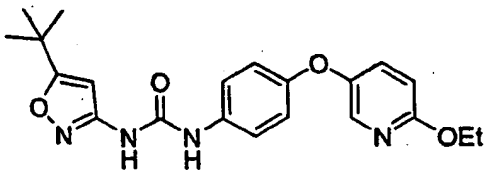


***N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-acetoxyphenyloxy)phenyl)urea:** To a solution of *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-hydroxyphenyloxy)phenyl)urea (0.100 g, 0.272 mmol), *N,N*-dimethylaminopyridine (0.003 g, 0.027 mmol) and Et_3N (0.075 mL, 0.544 mmol) in anh THF (5 mL) was added acetic anhydride (0.028 mL, 0.299 mmol), and the resulting mixture was stirred at room temp. for 5 h. The resulting mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (10 mL). The resulting solution was sequentially washed with a 5% citric acid solution (10 mL), a saturated $NaHCO_3$ solution (10 mL) and a saturated NaCl solution (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give an oil which slowly solidified to a glass (0.104 g, 93%) on standing under reduced pressure (approximately 0.4 mmHg): TLC (40% EtOAc/60% hexane) R_f 0.55; FAB-MS *m/z* 410 ($(M+H)^+$).

D9. Synthesis of ω-Alkoxypyridines

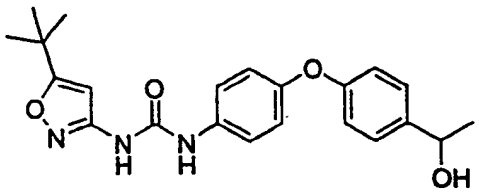


Step 1. *N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(2(1*H*)-pyridinon-5-yl)oxyphenyl)-urea: A solution of *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(5-(2-methoxy)pyridyl)-oxyaniline (prepared in a manner analogous to that described in Methods B3k and C3b; 1.2 g, 3.14 mmol) and trimethylsilyl iodide (0.89 mL, 6.28 mmol) in CH_2Cl_2 (30 mL) was allowed to stir overnight at room temp., then was to 40 °C for 2 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography (gradient from 80% EtOAc/20% hexans to 15% MeOH/85% EtOAc) to give the desired product (0.87 g, 75%): mp 175-180 °C; TLC (80% EtOAc/20% hexane) R_f 0.05; FAB-MS *m/z* 369 ($(M+H)^+$, 100%).



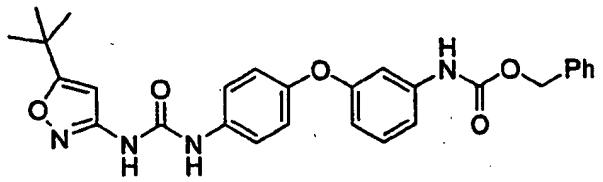
Step 2. ***N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(5-(2-Ethoxy)pyridyl)oxyphenyl)urea:** A slurry of *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(2(1*H*)-pyridinon-5-yl)oxyphenyl)urea (0.1 g, 0.27 mmol) and Ag_2CO_3 (0.05 g, 0.18 mmol) in benzene (3 mL) was stirred at room temp. for 10 min. Iodoethane (0.023 mL, 0.285 mmol) was added and the resulting mixture was heated at the reflux temp. in dark overnight. The reaction mixture was allowed to cool to room temp., and was filtered through a plug of Celite® then concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 25% EtOAc/75% hexane to 40% EtOAc/60% hexane) to afford the desired product (0.041 g, 38%): mp 146 °C; TLC (40% EtOAc/60% hexane) R_f 0.49; FAB-MS *m/z* 397 ($(M+H)^+$, 100%).

D10. Reduction of an Aldehyde- or Ketone-Containing Urea to a Hydroxide-Containing Urea



***N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-(1-hydroxyethyl)phenyl)oxyphenyl)urea:** To a solution of *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-(1-acetylphenyl)oxyphenyl)urea (prepared in a manner analogous to that described in Methods B1 and C2b; 0.060 g, 0.15 mmol) in MeOH (10 mL) was added $NaBH_4$ (0.008 g, 0.21 mmol) in one portion. The mixture was allowed to stir for 2 h at room temp., then was concentrated *in vacuo*. Water (20 mL) and a 3M HCl solution (2 mL) were added and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 10 mL) and a saturated NaCl solution (2 x 10 mL), dried ($MgSO_4$), and concentrated *in vacuo* . The resulting white solid was purified by trituration (Et_2O/hexane) to afford the desired product (0.021 g, 32 %): mp 80-85 °C; ^1H NMR (DMSO-d_6) δ 1.26 (s, 9H), 2.50 (s, 3H), 4.67 (m, 1H), 5.10 (br s, 1H), 6.45 (s, 1H), 6.90 (m, 4H), 7.29 (d, *J*=9.0 Hz, 2H), 7.42 (d, *J*=9.0 Hz, 2H), 8.76 (s, 1H), 9.44 (s, 1H); HPLC ES-MS *m/z* 396 ($(M+H)^+$).

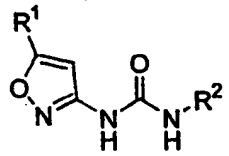
D11. Synthesis of Nitrogen-Substituted Ureas by Curtius Rearrangement of Carboxy-Substituted Ureas

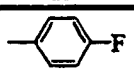
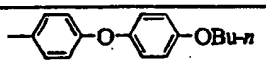
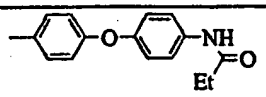
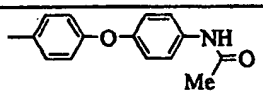
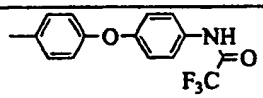
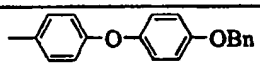
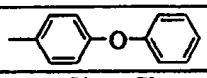
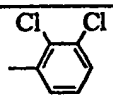
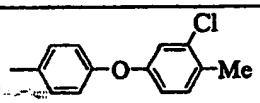
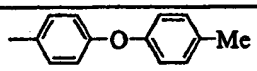
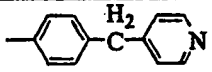


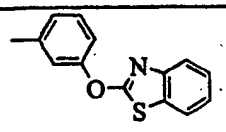
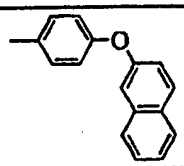
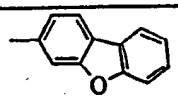
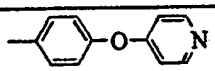
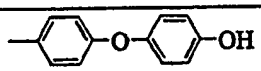
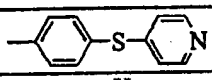
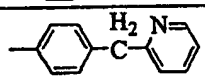
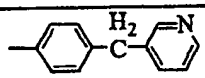
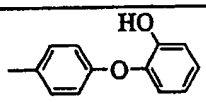
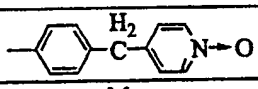
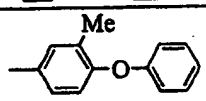
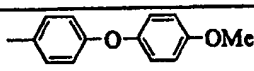
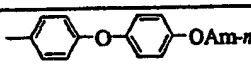
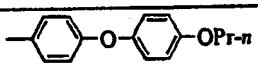
***N*-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-(benzyloxycarbonylamino)phenyl)-oxyphenyl)urea:** To a solution of the *N*-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(3-carboxyphenyl)oxyphenyl)urea (prepared in a manner analogous to that described in Methods B3a, Step 2 and C2b; 1.0 g, 2.5 mmol) in anh toluene (20 mL) was added Et_3N (0.395 mL, 2.8 mmol) and DPPA (0.610 mL, 2.8 mmol). The mixture was heated at 80 °C with stirring for 1.5 h then allowed to cool to room temp. Benzyl alcohol (0.370 mL, 3.5 mmol) was added and the mixture was heated at 80 °C with stirring for 3 h then allowed to cool to room temp. The resulting mixture was poured into a 10% HCl solution (50 mL) and teh resulting solution extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (3 x 50 mL) and a saturated NaCl (2 x 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude oil was purified by column chromatography (30% EtOAc/70% hexane) to afford the desired product as a white solid (0.7 g, 60 %): mp 73-75 °C; ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 9H), 5.10 (s, 2H), 6.46 (s, 1H), 6.55 (d, *J*=7.0 Hz, 1H), 6.94 (d, *J*=7.0 Hz, 2H), 7.70 (m, 7H), 8.78 (s, 1H), 9.46 (s, 1H), 9.81 (s, 1H); HPLC ES-MS *m/z* 501 ($(M+H)^+$).

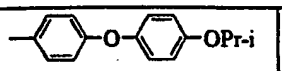
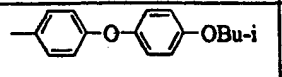
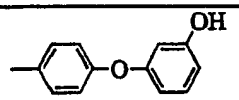
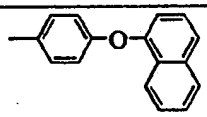
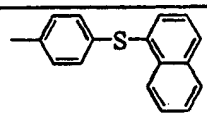
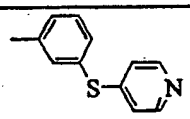
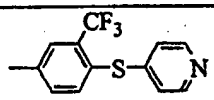
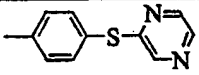
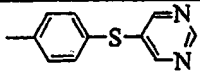
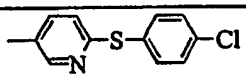
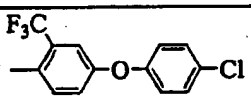
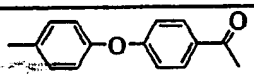
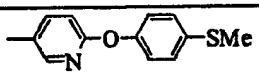
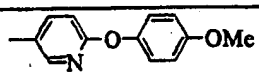
The following compounds have been synthesized according to the General Methods listed above:

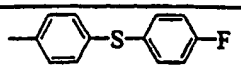
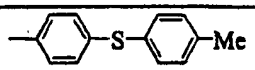
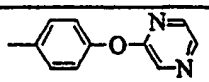
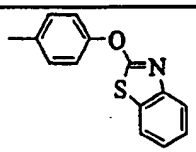
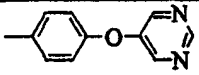
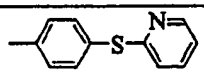
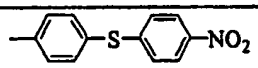
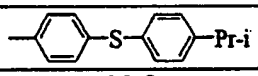
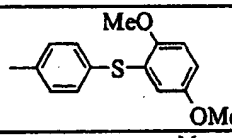
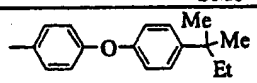
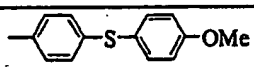
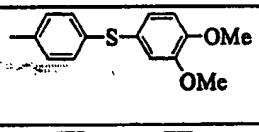
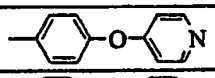
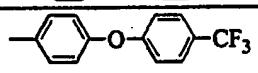
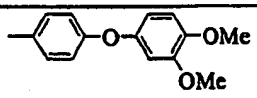
Table 1. 5-Substituted-3-isoxazolyl Ureas

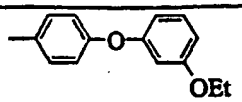
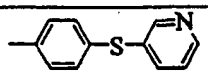
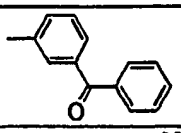
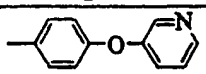
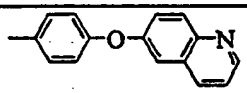
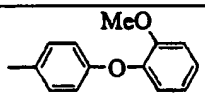
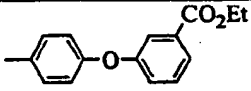
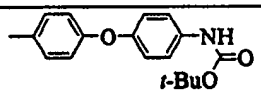
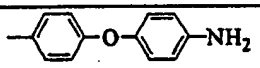
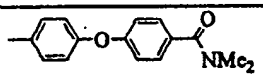
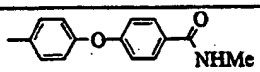
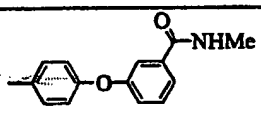
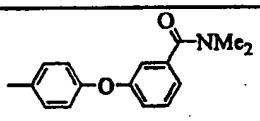
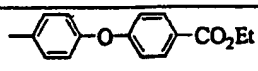


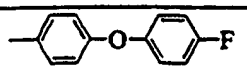
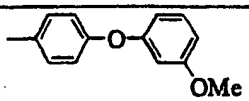
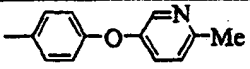
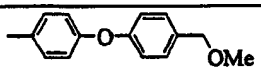
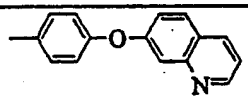
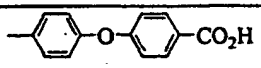
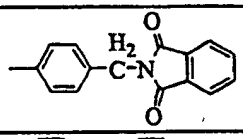
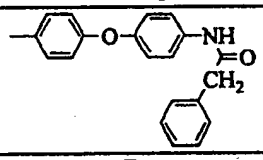
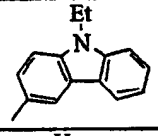
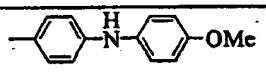
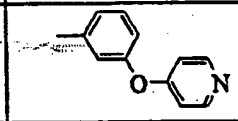
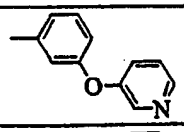
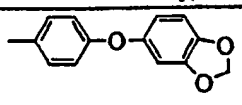
Ex.	R^1	R^2	mp (°C)	TLC R_f	Solvent System	Mass Spec.	Source	Synth. Method
1	*t*-Bu		169-172	0.45	25% EtOAc / 75% hexane	357 (M+H)+	FAB	C1b
2	*t*-Bu			0.63	5% MeOH / 95% CH2Cl2	288 (M+H)+	FAB	C2a
3	*t*-Bu		169-171			424 (M+H)+	FAB	C2b, D2
4	*t*-Bu			0.19	50% EtOAc / 50% hexane	423 (M+H)+	FAB	C2b, D3
5	*t*-Bu		202-206	0.15	60% EtOAc / 40% hexane	409 (M+H)+	FAB	C2b, D3
6	*t*-Bu		214-217	0.75	60% EtOAc / 40% hexane	463 (M+H)+	FAB	C2b, D3
7	*t*-Bu		157	0.42	40% EtOAc / 60% hexane	458 (M+H)+	FAB	B3a, C2b
8	*t*-Bu		148-149			352 (M+H)+	FAB	C1c
9	*t*-Bu			0.12	20% EtOAc / 80% hexane	329 (M+H)+	HPLC/ ES-MS	C1c
10	*t*-Bu		176-177	0.50	30% EtOAc / 70% hexane	400 (M+)	HPLC/ ES-MS	C2b
11	*t*-Bu		156-157	0.50	30% EtOAc / 70% hexane	366 (M+H)+	HPLC/ ES-MS	C2b
12	*t*-Bu		190-191	0.15	30% EtOAc / 70% hexane	350 (M+)	EI	C2b

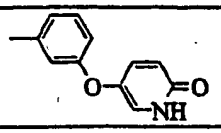
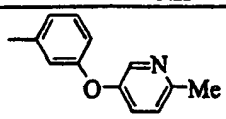
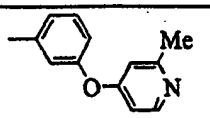
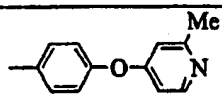
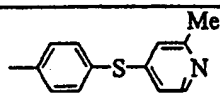
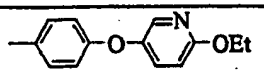
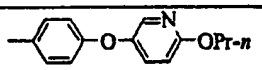
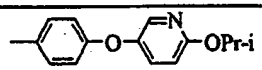
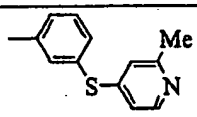
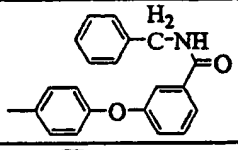
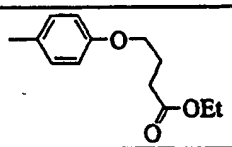
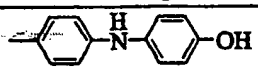
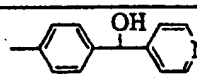
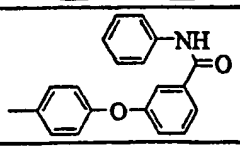
13	*t*-Bu		175-177	0.25	30% EtOAc / 70% hexane	409 (M+H)+	HPLC/ ES-MS	B3a Step 1, B3b Step 2, C2b
14	*t*-Bu			0.35	30% EtOAc / 70% hexane	402 (M+H)+	HPLC/ ES-MS	B3b, C2b
15	*t*-Bu			0.1	10% MeOH / 90% CH2Cl2	350 (M+H)+	HPLC/ ES-MS	C2b
16	*t*-Bu		240-243	0.2	15% MeOH / 85% EtOAc	352 (M+)	EI	C2b
17	*t*-Bu			0.15	30% EtOAc / 70% hexane	367 (M+)	EI	B3a, C2b, D2 Step 1
18	*t*-Bu		178-179			368 (M+)	EI	B4a, C2b
19	*t*-Bu		164-165	0.25	30% EtOAc / 70% hexane	351 (M+H)+	FAB	B1, C2b
20	*t*-Bu		170-172	0.15	30% EtOAc / 70% hexane	351 (M+H)+	FAB	B7, B1, C2b
21	*t*-Bu			0.3	25% EtOAc / 75% hexane	368 (M+H)+	FAB	C2b
22	*t*-Bu		188-191			367 (M+H)+	FAB	D7
23	*t*-Bu			0.8	25% EtOAc / 75% hexane	366 (M+H)+	FAB	B3a, C2b
24	*t*-Bu		155-156	0.55	30% EtOAc / 70% hexane	382 (M+H)+	FAB	B3a, C2b
25	*t*-Bu		145-148	0.6	25% EtOAc / 75% hexane	438 (M+H)+	FAB	B3a, C2b, D2
26	*t*-Bu		137-141	0.62	25% EtOAc / 75% hexane	410 (M+H)+	FAB	B3a, C2b, D2

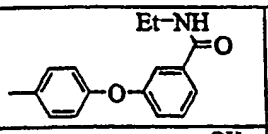
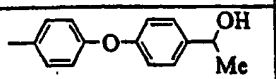
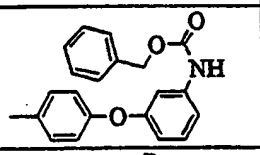
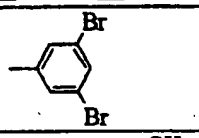
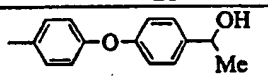
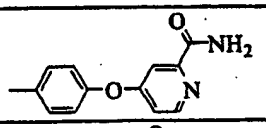
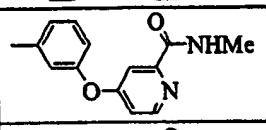
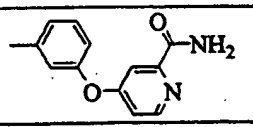
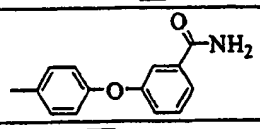
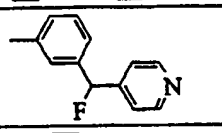
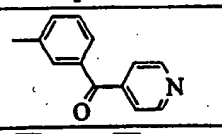
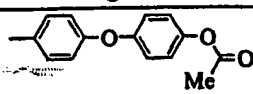
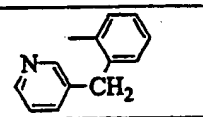
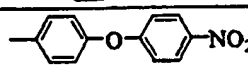
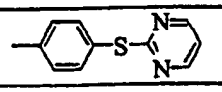
27	*t*-Bu		164-166	0.6	25% EtOAc / 75% hexane	410 (M+H)+	FAB	B3a, C2b, D2
28	*t*-Bu		69-71	0.6	25% EtOAc / 75% hexane	424 (M+H)+	FAB	B3a, C2b, D2
29	*t*-Bu		78-80	0.15	25% EtOAc / 75% hexane	368 (M+H)+	FAB	C2b
30	*t*-Bu		235	0.35	25% EtOAc / 75% hexane	402 (M+H)+	FAB	B3b, C2b
31	*t*-Bu		201-202	0.35	25% EtOAc / 75% hexane	418 (M+H)+	FAB	B3b, C2b
32	*t*-Bu		158-159	0.25	30% EtOAc / 70% hexane	369 (M+H)+	FAB	B4a, C2b
33	*t*-Bu		180-181	0.15	30% EtOAc / 70% hexane	437 (M+H)+	FAB	B3b, C2b
34	*t*-Bu		68-71	0.3	50% EtOAc / 50% hexane	370 (M+H)+	FAB	B4a, C2b
35	*t*-Bu		159-161	0.2	50% EtOAc / 50% hexane	370 (M+H)+	FAB	B4a, C2b
36	*t*-Bu		183-186	0.3	30% EtOAc / 70% hexane	403 (M+H)+	FAB	C2b
37	*t*-Bu		98-101	0.25	10% EtOAc / 90% hexane	454 (M+H)+	FAB	C2b
38	*t*-Bu		163-166	0.25	20% EtOAc / 80% hexane	394 (M+H)+	FAB	B1, C2b
39	*t*-Bu		144-147	0.3	30% EtOAc / 70% hexane	403 (M+H)+	FAB	C2b
40	*t*-Bu		155-157	0.25	10% EtOAc / 90% hexane	454 (M+H)+	FAB	C2b

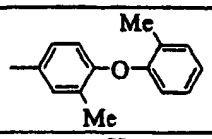
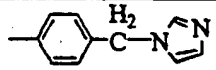
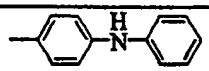
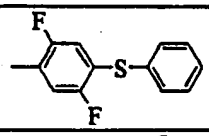
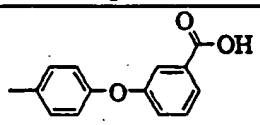
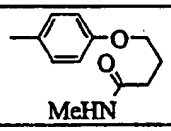
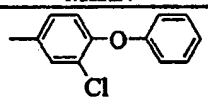
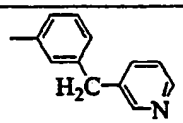
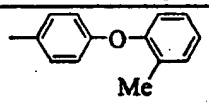
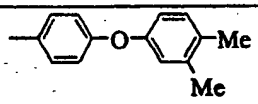
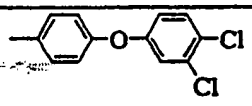
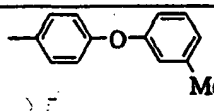
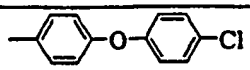
41	*t*-Bu		162-164	0.25	20% EtOAc / 80% hexane	394 (M+H)+	FAB	B1, C2b
42	*t*-Bu		149-150	0.15	15% EtOAc / 85% hexane	382 (M+H)+	FAB	C2b
43	*t*-Bu		200-201	0.35	50% EtOAc / 50% hexane	354 (M+H)+	FAB	B3j, C2b
44	*t*-Bu		77-80	0.3	30% EtOAc / 70% hexane	408 (M+)	EI	B3e, C2b
45	*t*-Bu		162-164	0.17	40% EtOAc / 60% hexane	354 (M+H)+	FAB	B3j, C2b
46	*t*-Bu		73-76	0.2	30% EtOAc / 70% hexane	368 (M+)	EI	B2, C2b
47	*t*-Bu		185-188	0.30	30% EtOAc / 70% hexane	413 (M+H)+	FAB	C2b
48	*t*-Bu		159-160			410 (M+H)+	FAB	B2, C2b
49	*t*-Bu		73-75	0.15	25% EtOAc / 75% hexane	428 (M+H)+	FAB	B2, C2b
50	*t*-Bu		188-190	0.25	5% EtOAc / 95% hexane	422 (M+H)+	FAB	B1, C2b
51	*t*-Bu		143-145	0.25	30% EtOAc / 70% hexane	398 (M+H)+	FAB	B3e, C2b
52	*t*-Bu		148-151	0.25	30% EtOAc / 70% hexane	428 (M+H)+	FAB	B3e, C2b
53	*t*-Bu			0.30	100% EtOAc	353 (M+H)+	FAB	B4b, C3b
54	*t*-Bu		172-174	0.25	10% EtOAc / 90% hexane	420 (M+H)+	FAB	C2b
55	*t*-Bu		126-129	0.25	30% EtOAc / 70% hexane	412 (M+H)+	FAB	B3e, C2b

56	*t*-Bu		201-204	0.25	10% EtOAc / 90% hexane	396 (M+H)+	FAB	B3e, C2b, D2
57	*t*-Bu		163-164	0.30	40% EtOAc / 60% hexane	369 (M+H)+	FAB	B4a, C2b
58	*t*-Bu		162-163	0.20	25% EtOAc / 75% hexane	363 (M+)	EI	C2b
59	*t*-Bu		127-129	0.22	40% EtOAc / 60% hexane	353 (M+H)+	FAB	B3e Step 1, B2, C2b
60	*t*-Bu		85-87	0.20	50% EtOAc / 50% hexane	402 (M+)	EI	B3e Step 1, B2, C2b
61	*t*-Bu		108-110	0.25	10% EtOAc / 90% hexane	381 (M+H)+	EI	B3e, C2b
62	*t*-Bu		153-155	0.25	30% EtOAc / 70% hexane	424 (M+H)+	FAB	B3e, C2b
63	*t*-Bu		117-120	0.25	10% EtOAc / 90% hexane	467 (M+H)+	FAB	B6, C2b
64	*t*-Bu		186-189	0.25	30% EtOAc / 70% hexane	367 (M+H)+	FAB	B6, C2b, D6
65	*t*-Bu		209-212	0.25	60% EtOAc / 40% hexane	423 (M+H)+	FAB	B3e, C2b, D5b
66	*t*-Bu		221-224	0.25	60% EtOAc / 40% hexane	409 (M+H)+	FAB	B3e, C2b, D5b
67	*t*-Bu		114-117	0.25	60% EtOAc / 40% hexane	409 (M+H)+	FAB	B3e, C2b, D5b
68	*t*-Bu		201-203	0.25	60% EtOAc / 40% hexane	423 (M+H)+	FAB	B3e, C2b, D5b
69	*t*-Bu		145-147	0.25	30% EtOAc / 70% hexane	423 (M+)	EI	B3e, C2b

70	*t*-Bu		148-151	0.25	20% EtOAc / 80% hexane	370 (M+H)+	FAB	B3e, C2b
71	*t*-Bu		188-201	0.25	20% EtOAc / 80% hexane	382 (M+H)+	FAB	B3e, C2b
72	*t*-Bu		134-136	0.25	20% EtOAc / 80% hexane	367 (M+H)+	FAB	B3e, C2b
73	*t*-Bu		152-155	0.25	20% EtOAc / 80% hexane	396 (M+H)+	FAB	B3e, C2b
74	*t*-Bu		176-178	0.25	50% EtOAc / 50% hexane	403 (M+H)+	FAB	B3e, C2b
75	*t*-Bu		200 dec	0.30	5% MeOH / 0.5% AcOH / 94.5% CH2Cl2	396 (M+H)+	FAB	B3a Step 2, C2b
76	*t*-Bu		177-180			419 (M+H)+	FAB	B8, B2b, C2b
77	*t*-Bu			0.60	60% EtOAc / 40% hexane	485 (M+H)+	FAB	C2b, D3
78	*t*-Bu		194-195	0.24	5% MeOH / 95% CH2Cl2	377 (M+H)+	FAB	C3a
79	*t*-Bu		160-162	0.79	75% EtOAc / 25% hexane	381 (M+H)+	FAB	C3a
80	*t*-Bu		140-143	0.25	50% EtOAc / 50% CH2Cl2	352 (M+)	EI	B4b, C3b
81	*t*-Bu		147-150	0.25	50% EtOAc / 50% CH2Cl2	352 (M+)	EI	B3f, C3b
82	*t*-Bu		166-170	0.44	50% EtOAc / 50% hexane	396 (M+H)+	FAB	C3b

83	*t*-Bu		175-180	0.05	80% EtOAc / 20% hexane	369 (M+H)+	FAB	B3k, C3b, D9
84	*t*-Bu		190-193	0.25	50% EtOAc / 50% CH2Cl2	367 (M+H)+	FAB	B3g, C3b
85	*t*-Bu		136-140	0.25	50% EtOAc / 50% CH2Cl2	367 (M+H)+	FAB	B4b, C3b
86	*t*-Bu		65-67	0.25	50% EtOAc / 50% CH2Cl2	367 (M+H)+	FAB	B4b, C3b
87	*t*-Bu		68-72	0.25	50% EtOAc / 50% CH2Cl2	383 (M+H)+	FAB	B4a, C3b
88	*t*-Bu		146	0.49	40% EtOAc / 60% hexane	397 (M+H)+	FAB	B3k, C3b, D9
89	*t*-Bu		100	0.54	40% EtOAc / 60% hexane	411 (M+H)+	FAB	B3k, C3b, D9
90	*t*-Bu		100	0.62	40% EtOAc / 60% hexane	411 (M+H)+	FAB	B3k, C3b, D9
91	*t*-Bu		164-165	0.25	50% EtOAc / 50% CH2Cl2	382 (M+)	EI	B4a, C3b
92	*t*-Bu		175-177	0.25	20% EtOAc / 80% hexane	485 (M+H)+	FAB	B3e, C3b, D5b
93	*t*-Bu		94-97	0.25	20% EtOAc / 80% hexane	390 (M+H)+	FAB	B5, C3b
94	*t*-Bu		137-141	0.30	50% EtOAc / 50% hexane	(M+)	EI	C3a, D2 step 1
95	*t*-Bu			0.15	100% EtOAc	367 (M+H)+	FAB	B9, C3a
96	*t*-Bu		120-122	0.25	20% EtOAc / 80% hexane	471 (M+H)+	HPLC ES-MS	B3e, C3b, D5b

97	*t*-Bu		168-170	0.25	50% EtOAc / 50% hexane	423 (M+H)+	HPLC ES-MS	B3e, C3b, D5b
98	*t*-Bu		80-85	0.25	50% EtOAc / 50% hexane	396 (M+H)+	HPLC ES-MS	B1, C2b, D10
99	*t*-Bu		73-75	0.25	30% EtOAc / 70% hexane	501 (M+H)+	HPLC ES-MS	B3a step 2, C2b, D11
100	*t*-Bu		240, DEC	414.95		414 (M+H)+	HPLC ES-MS	
101	*t*-Bu		132-134	0.52	40% EtOAc / 60% hexane	383 (M+H)+	FAB	B3a, B1, C3b
103	*t*-Bu			0.52	100% EtOAc	396 (M+H)+	HPLC / ES-MS	B10, B4b, C2b
104	*t*-Bu		107-110	0.85	100% EtOAc	410 (M+H)+	FAB	B10, B4b, C2b
105	*t*-Bu			0.75	100% EtOAc	396 (M+H)+	HPLC / ES-MS	B10, B4b, C2b
106	*t*-Bu		132-135					B3d step 2, C3a
107	*t*-Bu			0.45	100% EtOAc	369 (M+H)+	FAB	C2b
108	*t*-Bu			0.60	100% EtOAc	365 (M+H)+	FAB	C2b
109	*t*-Bu			0.55	40% EtOAc / 60% hexane	410 (M+H)+	FAB	B3b, C2b, D2 Step 1, D8
110	*t*-Bu		176-178					B7, C2a
111	*t*-Bu		195-197	0.30	25% EtOAc / 75% hexane	397 (M+)	FAB	C2b
112	*t*-Bu		179-182					B3b, C2a

113	*t*-Bu		78-82	0.25	10% EtOAc / 90% CH2Cl2	379 (M+)	EI	B3e, C3b
114	*t*-Bu		203-206	0.35	10% MeOH 0.5% AcOH / 89.5% EtOAc	340 (M+H)+	FAB	B8, B2b, C2b
115	*t*-Bu		189-191	0.20	30% EtOAc / 70% hexane	351 (M+H)+	FAB	C2b
116	*t*-Bu			0.60	5% acetone / 95% CH2Cl2	404 (M+H)+	FAB	B3b step 1,2, C1d
117	*t*-Bu		234 dec	0.30	5% MeOH / 0.5% AcOH / 94.5% CH2Cl2	396 (M+H)+	FAB	B3a Step 2, C2b
118	*t*-Bu		135-138					
119	*t*-Bu			0.13	5% acetone / 95% CH2Cl2	486 (M+H)+	FAB	B3b step 1,2, C1d
121	*t*-Bu		177-178	0.20	30% EtOAc / 70% hexane	351 (M+H)+	FAB	B7, B1, C2b
122	*t*-Bu			0.40	25% EtOAc / 75% hexane	366 (M+H)+	FAB	B3a, C2b
123	*t*-Bu		150-158	0.45	25% EtOAc / 75% hexane	380 (M+H)+	FAB	B3a, C2b
124	*t*-Bu		118-122	0.50	25% EtOAc / 75% hexane	420 (M+H)+	FAB	B3a Step 1, B3b Step 2, C2b
125	*t*-Bu		176-182	0.55	25% EtOAc / 75% hexane	366 (M+H)+	FAB	B3a, C2b
126	*t*-Bu		176-177	0.16	5% MeOH / 95% CH2Cl2	386 (M+H)+	FAB	C2b

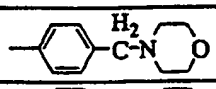
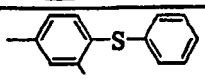
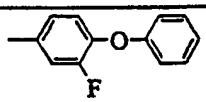
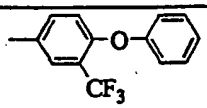
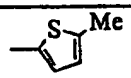
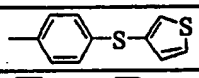
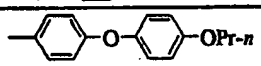
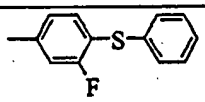
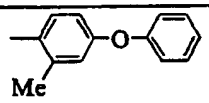
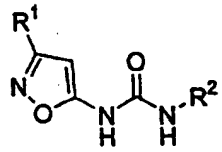
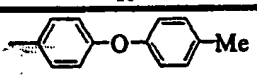
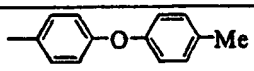
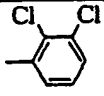
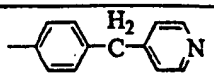
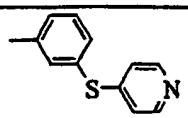
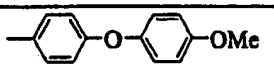
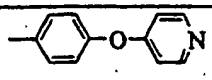
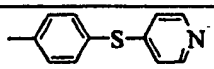
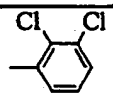
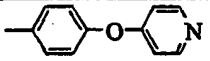
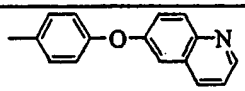
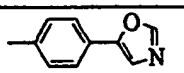
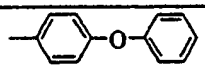
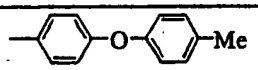
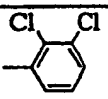
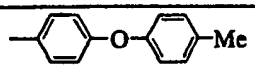
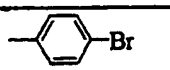
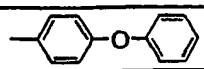
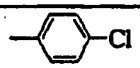
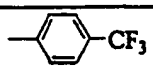
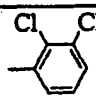
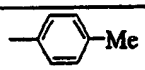
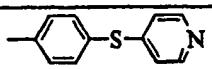
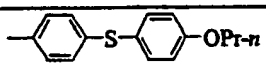
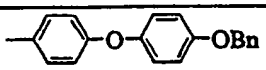
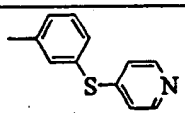
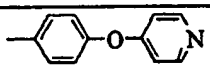
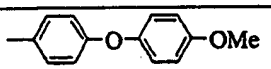
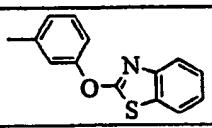
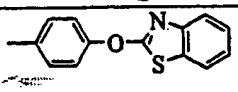
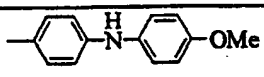
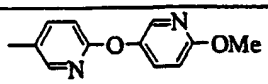
127	*t*-Bu		195-198					B8, C2a
128	*t*-Bu		141-144	0.63	5% acetone / 95% CH2Cl2	381 (M+H)+	FAB	B3b step 1,2, C1d
129	*t*-Bu		145-148	0.44	5% acetone / 95% CH2Cl2	369 (M+H)+	FAB	B3b step 1,2, C1d
131	*t*-Bu		199-200	0.59	5% acetone / 95% CH2Cl2	419 (M+)	FAB	B1a
132	*t*-Bu		200-201	0.20	20% EtOAc / 80% hexane	280 (M+H)+	FAB	C1b
133	*t*-Bu		167-169			374 (M+H)+	FAB	B3i, B1, C2b
134	*t*-Bu		137-141	0.62	25% EtOAc / 75% hexane	410 (M+H)+	FAB	B3a, C2b, D2
135	*t*-Bu			0.57	5% acetone / 95% CH2Cl2	386 (M+H)+	FAB	B3b step 1,2, C1d
136	*t*-Bu			0.50	5% acetone / 95% CH2Cl2	366 (M+H)+	FAB	B1a

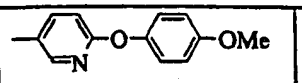
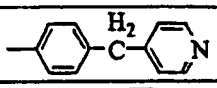
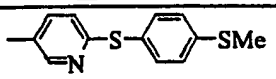
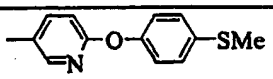
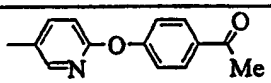
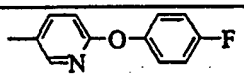
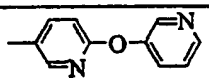
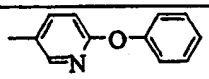
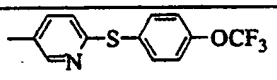
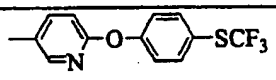
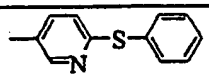
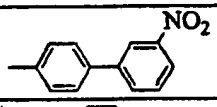
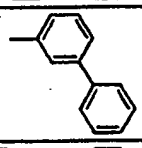
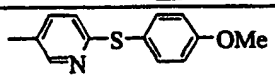
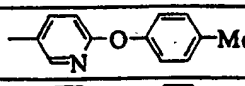
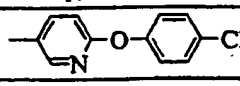
Table 2. 3-Substituted-5-isoxazolyl Ureas

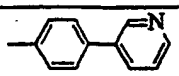
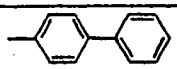
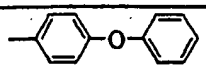
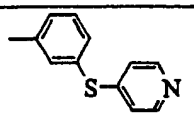
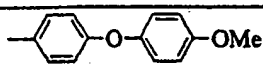
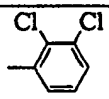
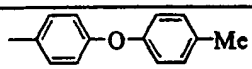
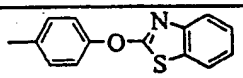
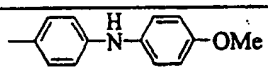
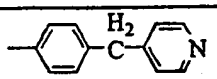
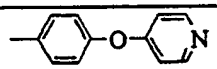
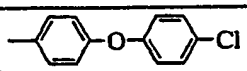
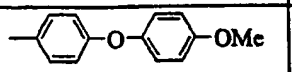
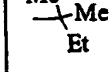
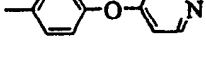
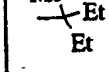
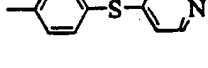


Ex.	R^1	R^2	mp (°C)	TLC R_f	Solvent System	Mass Spec.	Source	Synth. Method
137	Me		169-170	0.25	5% acetone / 95% CH2Cl2	324 (M+H)+	FAB	C1b
138	i-Pr		166-170	0.54	50% EtOAc / 50% pet ether	352 (M+H)+	FAB	C1b
139	i-Pr		148-149	0.40	5% acetone / 95% CH2Cl2	313 (M+)	EI	C1b

140	i-Pr		272 dec	0.21	5% MeOH / 95% CHCl3	337 (M+H)+	FAB	A2, C3a
141	i-Pr			0.25	5% MeOH / 95% CHCl3	355 (M+H)+	FAB	A2, B4a, C3a
142	i-Pr			0.14	30% EtOAc / 70% pet ether	368 (M+H)+	FAB	A2, B3a, C3a
143	i-Pr		75-77 dec	0.22	5% MeOH / 95% CH2Cl2	339 (M+H)+	FAB	A2, C3a
144	i-Pr		112-117	0.29	5% MeOH / 95% CH2Cl2	355 (M+H)+	FAB	A2, B4a, C3a
145			171	0.33	5% acetone / 95% CH2Cl2	326 (M+H)+	FAB	C1b
146						351 (M+H)+	HPLC / ES-MS	C8
147				0.03	50% EtOAc / 50% hexane	401 (M+H)+	FAB	C8
148			159-160	0.22	5% EtOAc/ 95% hexane	325 (M+H)+	HPLC / ES-MS	C4a
149			190-191	0.38	50% EtOAc / 50% pet ether	350 (M+H)+	FAB	C1b
150			175-178	0.43	50% EtOAc / 50% pet ether	364 (M+H+)	FAB	C1b
151	*n*-Bu		133	0.37	5% acetone / 95% CH2Cl2	328 (M+H)+	FAB	C1b
152	*t*-Bu		165 dec	0.34	40% EtOAc / 60% pet ether	366 (M+H+)	FAB	C1b
153	*t*-Bu		188-189	0.82	5% acetone / 95% CH2Cl2	338 (M+H)+	FAB	C1b
154	*t*-Bu		182-184			352 (M+H)+	FAB	C1b

155	*t*-Bu			0.65	5% MeOH / 95% CH2Cl2	294 (M+H)+	FAB	C2a
156	*t*-Bu			0.25	3% MeOH / 97% CH2Cl2	328 (M+H)+	FAB	C2a
157	*t*-Bu			0.57	3% MeOH / 97% CH2Cl2	328 (M+H)+	FAB	C2a
158	*t*-Bu			0.60	5% MeOH / 95% CH2Cl2	274 (M+H)+	FAB	C2a
159	*t*-Bu			0.21	5% MeOH / 95% CH2Cl2	369 (M+H)+	FAB	B4a, C2a
160	*t*-Bu			0.52	50% EtOAc / 50% hexane	426 (M+H)+	FAB	B5, C4a
161	*t*-Bu			0.36	40% EtOAc / 60% hexane	458 (M+H)+	FAB	B3a, C2b
162	*t*-Bu		213 dec	0.05	5% acetone / 95% CH2Cl2	369 (M+H)+	FAB	C3a
163	*t*-Bu		210 dec	0.05	5% acetone / 95% CH2Cl2	353 (M+H)+	FAB	C3a
164	*t*-Bu		174-175	0.25	5% acetone / 95% CH2Cl2	382 (M+H)+	FAB	C3a
165	*t*-Bu		90-92	0.16	5% acetone / 95% CH2Cl2	409 (M+H)+	FAB	C2a
166	*t*-Bu		221 dec	0.14	5% acetone / 95% CH2Cl2	409 (M+H)+	FAB	C2a
167	*t*-Bu		182	0.28	40% EtOAc / 60% hexane	380 (M+)	EI	A2, C3a
168	*t*-Bu		196-198	0.17	5% MeOH / 95% CH2Cl2	368 (M+H)+	FAB	A2, B3h, C3a

169	*t*-Bu		204-206	0.27	50% EtOAc / 50% pet ether	383 (M+H)+	FAB	A2, B3a, C3a
170	*t*-Bu		179-180			351 (M+H)+	FAB	A2, C3a
171	*t*-Bu			0.33	50% EtOAc / 50% pet ether	414 (M+)	EI	A2, B4a, C3a
172	*t*-Bu		188-189	0.49	50% EtOAc / 50% pet ether	399 (M+H)+	HPLC ES-MS	A2, B4a, C3a
173	*t*-Bu		179-180	0.14	5% MeOH / 95% CH2Cl2	395 (M+H)+	FAB	A2, B4a, C3a
174	*t*-Bu		118-121	0.19	5% MeOH / 95% CH2Cl2	387 (M+H)+	FAB	A2, B4a, C3a
175	*t*-Bu		197-199	0.08	10% acetone / 90% CH2Cl2	353 (M+H)+	FAB	A2, B3h, C3a
176	*t*-Bu		208-212	0.17	5% MeOH / 95% CH2Cl2	353 (M+H)+	FAB	C3b
177	*t*-Bu		155-156	0.57	10% MeOH / CH2Cl2	453 (M+H)+	FAB	C3b
178	*t*-Bu		163-165	0.21	5% MeOH / 95% CH2Cl2	453 (M+H)+	HPLC / ES-MS	C3b
179	*t*-Bu		109-112	0.17	5% MeOH / 95% CH2Cl2	369 (M+H)+	FAB	C3b
180	*t*-Bu		199-202	0.60	5% MeOH / CH2Cl2			C3b
181	*t*-Bu		160-162	0.58	50% EtOAc / 50% pet ether	336 (M+)	CI	C3b
182	*t*-Bu			0.18	50% EtOAc / 50% pet ether			C3b
183	*t*-Bu		180					C3b
184	*t*-Bu		214-217					C3b

185	*t*-Bu			0.13	50% EtOAc / 50% hexane	337 (M+H) +	CI	C3b
186	*t*-Bu		154-156	0.51	50% EtOAc / 50% pet ether	336 (M+H) +	FAB	C3b
187			154-155	0.50	50% EtOAc / 50% pet ether	365 (M+)	EI	C1b
188			215-221 dec	0.05	5% acetone / 95% CH2Cl2	383 (M+H)+	FAB	C3a
189			137-138	0.25	5% acetone / 95% CH2Cl2	396 (M+H)+	FAB	C3a
190			196-199	0.58	5% acetone / 95% CH2Cl2	342 (M+H+)	FAB	C1b
191			160-162	0.37	5% acetone / 95% CH2Cl2	380 (M+H+)	FAB	C1b
192			199-200	0.33	70% EtOAc / 30% pet ether	468 (M+)+	FAB	A2, B3e, C3a
193			161-162	0.28	40% EtOAc / 60% hexane	394 (M+)	EI	A2, C3a
194				0.18	5% MeOH / 95% CHCl3	364 (M+)	EI	A2, C3a
195			90-92	0.19	30% EtOAc / 70% pet ether	232 (M+)	EI	A2, C3a
196			180-181	0.26	30% EtOAc / 70% pet ether			A2, C3b
197			63-65			410 (M+H)+	FAB	A2, B3a, C3a
198			84	0.16	5% MeOH / 95% CHCl3	381 (M+H)+	FAB	A2, C3a
199			189-192	0.16	5% MeOH / 95% CHCl3	397 (M+H)+	HPLC EI-MS	A2, B4a, C3a

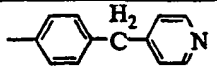
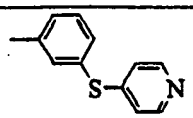
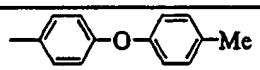
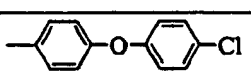
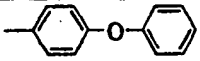
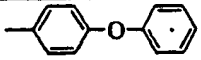
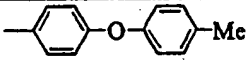
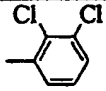
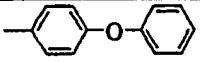
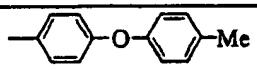
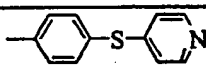
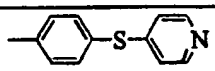
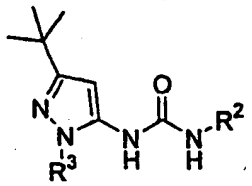
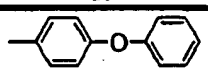
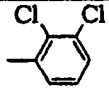
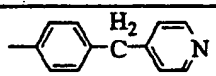
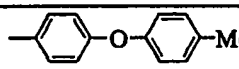
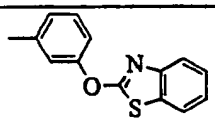
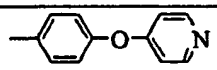
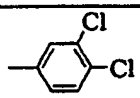
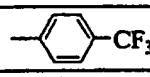
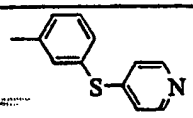
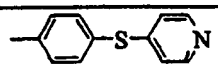
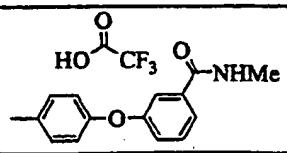
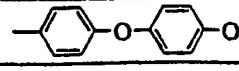
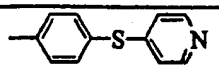
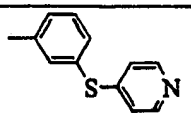
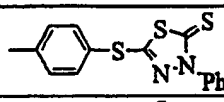
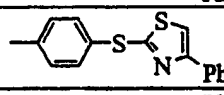
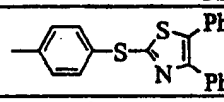
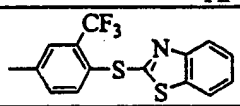
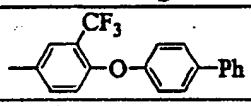
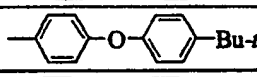
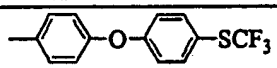
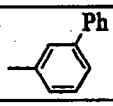
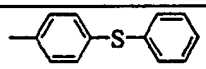
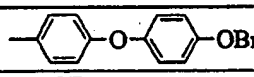
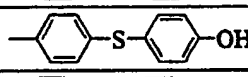
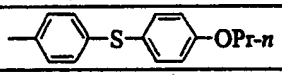
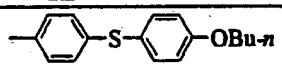
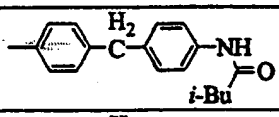
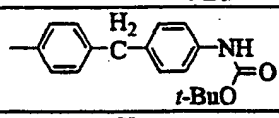
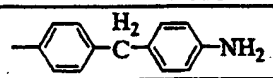
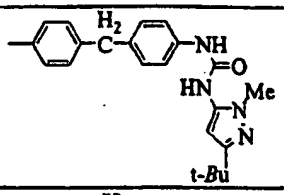
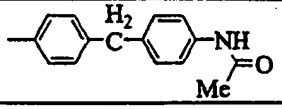
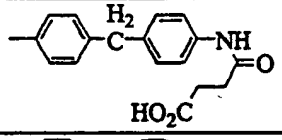
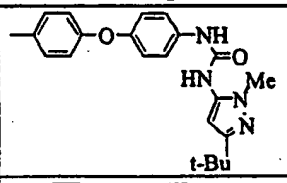
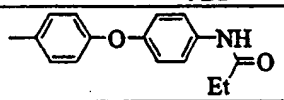
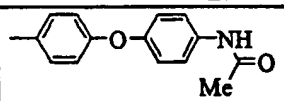
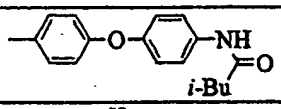
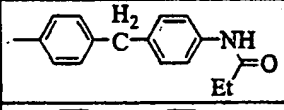
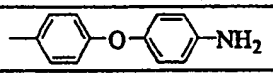
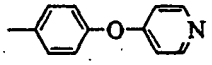
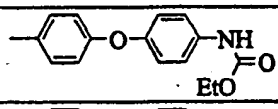
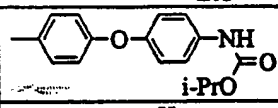
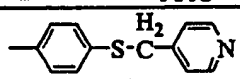
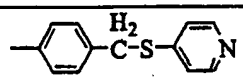
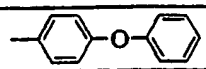
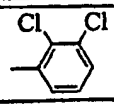
200			175-177	0.16	5% MeOH / 95% CHCl3	379 (M+H)+	FAB	A2, C3a
201			189-191	0.17	5% MeOH / 95% CHCl3	397 (M+H)+	FAB	A2, B4a, C3a
202			67	0.41	5% MeOH / 95% CHCl3			A2, C3b
203			123-125			414 (M+H)+	FAB	A2, C3a
204			135-137	0.33	5% MeOH / 95% CHCl3			A2, C3b
205			178-180	0.39	5% acetone / 95% CH2Cl2	366 (M+H+)	FAB	C1b
206			200-202	0.44	5% acetone / 95% CH2Cl2	380 (M+H)+	FAB	C1b
207			150-154	0.39	5% acetone / 95% CH2Cl2	342 (M+H)+	FAB	C1b
208			155-156	0.38	50% EtOAc / 50% pet ether	377 (M+)	EI	C1b
209	Ph			0.33	5% acetone / 95% CH2Cl2	386 (M+H)+	FAB	C1b
210			190-191	0.23	5% MeOH / 95% CH2Cl2	395 (M+H)+	FAB	A2, B4a, C3a
211				0.18	5% MeOH / 95% CHCl3	379 (M+H)+	FAB	A2, C3b

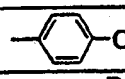
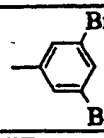
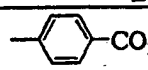
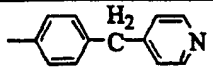
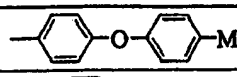
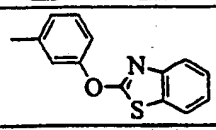
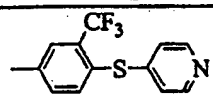
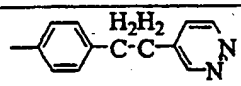
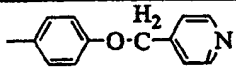
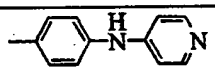
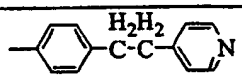
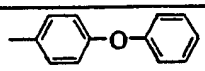
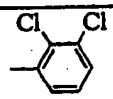
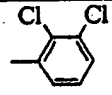
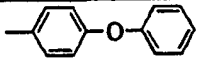
Table 3. N^1-Substituted-3-*tert*-butyl-5-pyrazolyl Ureas



Ex.	R^1	R^2	mp (°C)	TLC R_f	Solvent System	Mass Spec.	Source	Synth. Method
212	H			0.27	50% EtOAc / 50% hexane	351 (M+H)+	FAB	C1c
213	H			0.59	50% EtOAc / 50% hexane	327 (M+H)+	FAB	C1c
214	H			0.30	60% acetone / 40% CH2Cl2	350 (M+H)+	FAB	C4a
215	H		204	0.06	5% acetone / 95% CH2Cl2	364 (M+)	EI	C3b
216	H		110-111	0.05	5% acetone / 95% CH2Cl2	408 (M+H+)	FAB	C3b
217	H		228-232 dec	0.24	10% MeOH / 90% CHCl3	351 (M+)	EI	C3a
218	H		182-184	0.05	40% EtOAc / 60% hexane	327 (M+H)+	FAB	A5, C1e
219	H		110-112			326 (M+)	EI	A5, C1e
220	H			0.07	5% MeOH / 95% CHCl3	368 (M+H)+	FAB	B4a, C4a
221	H			0.18	5% MeOH / 95% CHCl3	364 (M+)	EI	B4a, C4a
222	H		160-161			408 (M+H)+	FAB	A5, B6, C3b isolated at TFA salt
223	H		181-183			381 (M+H)+	FAB	C2b

224	Me			0.35	70% acetone / 30% CH2Cl2	382 (M+H)+	FAB	B4a, C4a
225	Me			0.46	70% acetone / 30% CH2Cl2	382 (M+H)+	FAB	C4a, B4a
226	Me			0.47	100% EtOAc	497 (M+H)+	FAB	B3c, C4a
227	Me			0.46	100% EtOAc	464 (M+H)+	FAB	B3c, C4a
228	Me			0.50	100% EtOAc	540 (M+H)+	FAB	B3c, C4a
229	Me			0.52	100% EtOAc	506 (M+H)+	FAB	B3c, C4a
230	Me			0.51	100% EtOAc	509 (M+H)+	FAB	B3c, C4a
231	Me			0.75	100% EtOAc	421 (M+H)+	FAB	B3c, C4a
232	Me			0.50	100% EtOAc	465 (M+H)+	FAB	B3c, C4a
233	Me			0.50	100% EtOAc	349 (M+H)+	FAB	C4a
234	Me			0.09	50% EtOAc / 50% hexane	381 (M+H)+	FAB	C4a
235	Me			0.60	100% EtOAc	471 (M+H)+	FAB	B2, C4a
236	Me			0.61	100% EtOAc	397 (M+H)+	FAB	B3c, C4a
237	Me			0.42	100% EtOAc	439 (M+H)+	FAB	B5, C4a
238	Me			0.25	50% EtOAc / 50% hexane	453 (M+H)+	FAB	B5, C4a
239	Me			0.65	100% EtOAc	462 (M+H)+	FAB	B6, C4a
240	Me			0.67	100% EtOAc	478 (M+H)+	FAB	B6, C4a
241	Me			0.50	100% EtOAc	378 (M+H)+	FAB	C4a

242	Me			0.30	100% EtOAc	557 (M+H)+	FAB	C4a
243	Me			0.33	100% EtOAc	420 (M+H)+	FAB	C4a, D3
244	Me			0.60	10% water / 90% CH3CN	478 (M+H)+	FAB	C4a, D3
245	Me			0.28	100% EtOAc	559 (M+H)+	FAB	C4a
246	Me			0.40	100% EtOAc	436 (M+H)+	FAB	C4a, D3
247	Me			0.46	50% acetone / 50% CH2Cl2	422 (M+H)+	FAB	C4a, D3
248	Me			0.50	100% EtOAc	464 (M+H)+	FAB	C4a, D3
249	Me			0.55	100% EtOAc	434 (M+H)+	FAB	C4a, D3
250	Me			0.52	100% EtOAc	380 (M+H)+	FAB	C4a
251	Me			0.25	60% acetone / 40% CH2Cl2	366 (M+H)+	FAB	C4a
252	Me			0.52	100% EtOAc	452 (M+H)+	FAB	C4a, D3
253	Me			0.52	100% EtOAc	466 (M+H)+	FAB	C4a, D3
254	Me			0.34	60% acetone / 40% CH2Cl2	396 (M+H)+	FAB	C4a
255	Me			0.36	60% acetone / 40% CH2Cl2	396 (M+H)+	FAB	C4a
256	Me		147-149			365 (M+H)+	FAB	C1c
257	Me		173-175			341 (M+H)+	FAB	C1c

258	Me		185-187			341 (M+H)+	HPLC / ES-MS	C1c
259	Me		195-197			429 (M+H)+	FAB	C1c
260	Me			0.25	50% EtOAc / 50% hexane	373 (M+H)+	FAB	C1c
261	Me		161-162	0.15	4% MeOH / 96% CH2Cl2	364 (M+H)+	FAB	C2b
262	Me		228 dec			379 (M+H)+	FAB	C2b
263	Me			0.30	5% MeOH / 95% CH2Cl2	422 (M+H)+	FAB	C2b
264	Me			0.32	70% acetone / 30% CH2Cl2	450 (M+H)+	FAB	B3b, C4a
265	Me			0.15	40% acetone / 60% CH2Cl2	379 (M+H)+	FAB	B1, B2, C3a
266	Me			0.10	20% acetone / 80% CH2Cl2	380 (M+H)+	FAB	C4a
267	Me			0.20	80% EtOAc / 20% hexane	365 (M+H)+	FAB	C3a
268	Me			0.48	30% acetone / 70% CH2Cl2	378 (M+H)+	FAB	B1, C3a
269	$-CH_2CF_3$			0.22	30% EtOAc / 70% hexane	433 (M+H)+	FAB	A3, C1b
270	$-CH_2CF_3$			0.38	30% EtOAc / 70% hexane	409 (M+H)+	FAB	A3, C1b
271	$-(CH_2)_2CN$			0.53	70% EtOAc / 30% hexane	380 (M+)	HPLC / ES-MS	A3, C1b
272	$-(CH_2)_2CN$			0.37	70% EtOAc / 30% hexane	404 (M+H)+	HPLC / ES-MS	A3, C1b

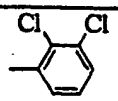
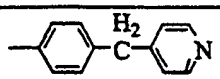
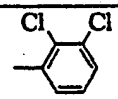
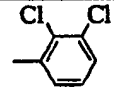
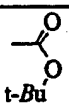
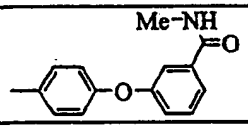
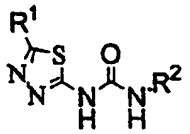
273	-$(CH_2)_2OH$			0.15	60% EtOAc / 40% hexane	371 (M+H)+	FAB	A3, C1b, D4
274				0.49	40% acetone / 60% CH2Cl2	432 (M+H)+	FAB	A3, C4a
275	-CH_2CO_2Et			0.44	50% EtOAc / 50% hexane	413 (M+H)+	FAB	A3, C1b
276				0.59	60% acetone / 40% CH2Cl2	398 (M+H)+	FAB	A3, C1b, D5a
277			159-161			508 (M+H)+	FAB	A5, B6, C2b

Table 4. 5-Substituted-2-thiadiazolyl Ureas



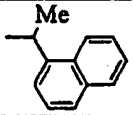
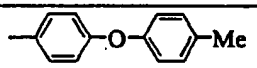
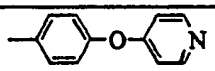
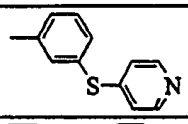
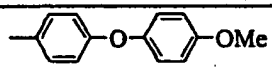
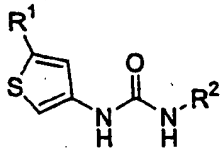
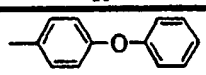
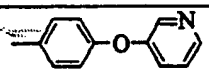
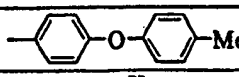
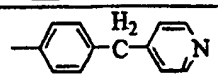
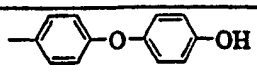
Ex.	R^1	R^2	mp (°C)	TLC R_f	Solvent System	Mass Spec.	Source	Synth. Method
278	*t*-Bu		243-244			355 (M+H)+	HPLC / ES-MS	C1c
279	*t*-Bu			0.30	5% acetone / 95% CH2Cl2	383 (M+H)+	FAB	C1b
280	*t*-Bu			0.26	5% MeOH / 95% CH2Cl2	370 (M+H)+	FAB	C3a
281	*t*-Bu					386 (M+H)+	FAB	B4a, C3a
282	*t*-Bu			0.37	5% MeOH / 95% CH2Cl2	399 (M+H)+	FAB	B3a, C3a

Table 5. 5-Substituted-3-thienyl Ureas



Ex.	R^1	R^2	mp (°C)	TLC R_f	Solvent System	Mass Spec.	Source	Synth. Method
283	*t*-Bu		144-145	0.68	5% acetone / 95% CH2Cl2			A4b, C1a
284	*t*-Bu			0.28	50% Et2O / 50% pet ether	368 (M+H)+	HPLC / ES-MS	A4a
285	*t*-Bu		57			381 (M+H)+	FAB	A4a
286	*t*-Bu			0.15	50% EtOAc / 50% pet ether	365 (M+)	EI	A4a
287	*t*-Bu			0.44	50% EtOAc / 50% pet ether	383 (M+H)+	FAB	A4a

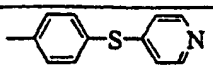
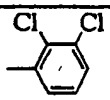
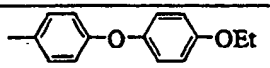
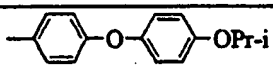
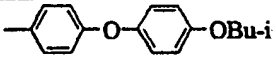
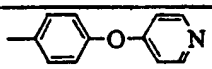
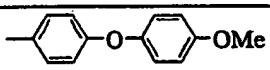
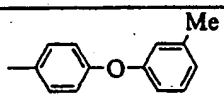
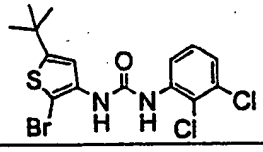
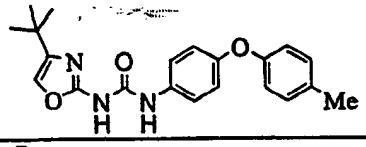
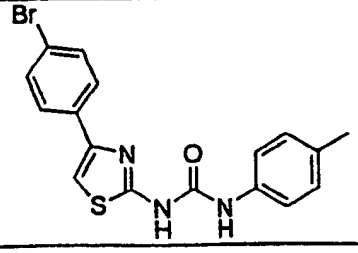
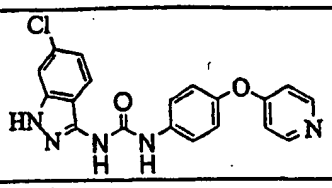
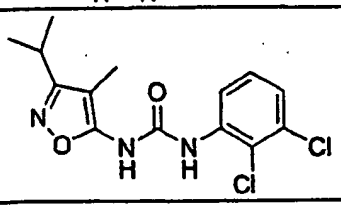
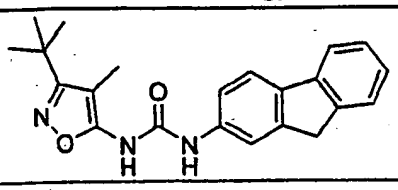
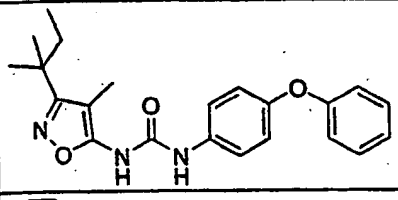
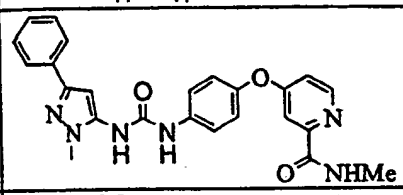
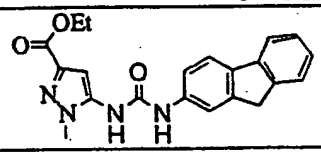
288	*t*-Bu			0.36	50% EtOAc / 50% pet ether	384 (M+H)+	FAB	A4a
289	*t*-Bu		169-170	0.57	20% EtOAc / 80% hexane	343 (M+H)+	FAB	A4c, C1d
290	*t*-Bu		155-156	0.40	20% EtOAc / 80% hexane	411 (M+H)+	FAB	D2
291	*t*-Bu		165-166	0.40	20% EtOAc / 80% hexane	425 (M+H)+	FAB	D2
292	*t*-Bu		188-189	0.45	20% EtOAc / 80% hexane	439 (M+H)+	FAB	D2
293	*t*-Bu			0.13	50% EtOAc / 50% hexane	368 (M+H)+	FAB	A4c, C4c
294	*t*-Bu			0.26	30% Et2O / 70% pet ether	397 (M+H)+	HPLC / ES-MS	A4c, C1d
295	*t*-Bu			0.52	30% Et2O / 70% pet ether	381 (M+H)+	HPLC / ES-MS	A4a

Table 5. Additional Ureas

Ex.	R^2	mp (°C)	TLC R_f	Solvent System	Mass Spec.	Source	Synth. Method
296		161-163	0.71	20% EtOAc / 80% hexane	367 (M+H)+	FAB	D1
297		162-164	0.52	30% EtOAc / 70% hexane	365 (M+H)+	FAB	A8, C1d
298			0.67	5% acetone / 95% CH2Cl2	388 (M+H)+	FAB	C1b

299			0.72	90% EtOAc / 10% hexane	380 (M+H) +	HPLC / ES	MS B4b, C4a
300		170-172	0.40	5% acetone / 95% CH2Cl2	328 (M+H)+	FAB	C1b
301		179-181			362 (M+H)+	HPLC / ES-MS	C5
302		155-157	0.44	5% acetone / 95% CH2Cl2	380 (M+H+)	FAB	C1b
302			0.55	90% EtOAc / 10% hexane	443 (M+H)+	FAB	B10, B4b, C2b
303		230 dec			377 (M+H)+	HPLC / ES-MS	C5

BIOLOGICAL EXAMPLES

P38 Kinase Assay:

The *in vitro* inhibitory properties of compounds were determined using a p38 kinase inhibition assay. P38 activity was detected using an *in vitro* kinase assay run in 96-well microtiter plates. Recombinant human p38 (0.5 µg/mL) was mixed with substrate (myelin basic protein, 5 µg/mL) in kinase buffer (25 mM Hepes, 20 mM $MgCl_2$ and 150 mM NaCl) and compound. One µCi/well of ^{33}P-labeled ATP (10 µM) was added to a final volume of 100 µL. The reaction was run at 32 °C for 30 min. and stopped with a 1M HCl solution. The amount of radioactivity incorporated into the substrate was determined by trapping the labeled substrate onto negatively charged glass fiber filter paper using a 1% phosphoric acid solution and read with a scintillation counter. Negative controls include substrate plus ATP alone.

All compounds exemplified displayed p38 IC_{50}s of between 1 nM and 10 μM.

LPS Induced TNF Production in Mice:

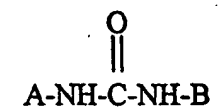
The *in vivo* inhibitory properties of selected compounds were determined using a murine LPS induced TNFα production *in vivo* model. BALB/c mice (Charles River Breeding Laboratories; Kingston, NY) in groups of ten were treated with either vehicle or compound by the route noted. After one hour, endotoxin (E. coli lipopolysaccharide (LPS) 100 μg was administered intraperitoneally (i.p.). After 90 min, animals were euthanized by carbon dioxide asphyxiation and plasma was obtained from individual animals by cardiac puncture ionto heparinized tubes. The samples were clarified by centrifugation at 12,500 x *g* for 5 min at 4 °C. The supernatants were decanted to new tubes, which were stored as needed at -20 °C. TNFα levels in sera were measured using a commercial murine TNF ELISA kit (Genzyme).

The preceeding examples can be repeated with similar success by substituting the generically of specifically described reactants and/or operating conditions of this invention for those used in the preceeding examples

From the foregoing discussion, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A method for the treatment of a disease mediated by p38 other than cancer, comprising administering a compound of formula I



I

wherein B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10}

cycloalkyl, up to per-halosubstituted C_2-C_{10} alkenyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is -O-, -S-, -N(R^5)-, -$(CH_2)_m$-, -C(O)-, -CH(OH)-, -$(CH_2)_m$O-, -$(CH_2)_m$S-, -$(CH_2)_m$N(R^5)-, -O$(CH_2)_m$-, -CHX^a, -NR^5C(O)NR^5 $R^{5'}$-, -NR^5C(O)-, -C(O)NR^5-, -CX^a_2-, -S-$(CH_2)_m$- and -N(R^5)$(CH_2)_m$-,

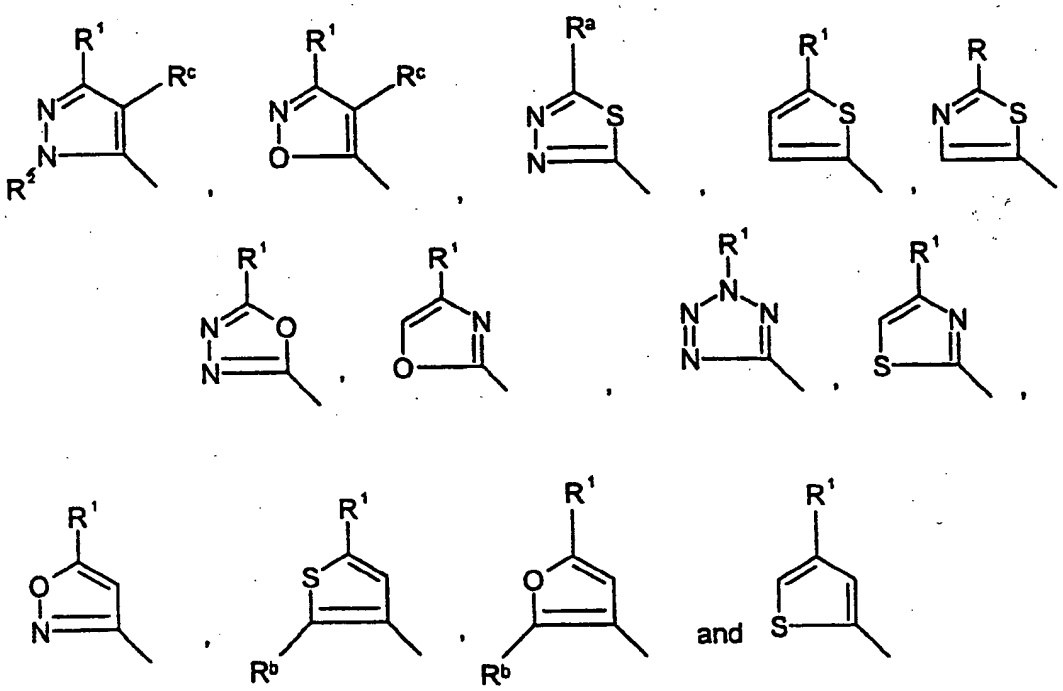
m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1},

wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, -CO_2R^5, -C(O)$NR^5R^{5'}$, -C(O)- NR^5, -NO_2, =O, -OR^5, - SR^5, - $NR^5R^{5'}$, -C(O)R^5, -SO_2R^5, -$SO_2NR^5R^{5'}$, -NR^5C(O)$OR^{5'}$, -NR^5C(O)$R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, -CO_2R^5, -C(O)$R^{5'}$,-C(O)$NR^5R^{5'}$, =O, -OR^5, -SR^5, -NO_2, -$NR^5R^{5'}$, -NR^5C(O)$R^{5'}$, -NR^5C(O)$OR^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C-C_{10} heteroaryl, C_6-C_{14} aryl, C_4-C_{24} alkheteroaryl and C_7-C_{24} alkaryl.

A is a heteroaryl moiety selected from the group consisting of



wherein

R^1 is selected from the group consisting of halogen, C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl;

R^2 is selected from the group consisting of H, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^3R^{3'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl,

where R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^4$, $-C(O)-NR^3R^{3'}$, $-NO_2$, $-OR^4$, $-SR^4$, and halogen up to per-halosubstitution,

wherein R^3 and $R^{3'}$ are independently selected from the group consisting of H, $-OR^4$, $-SR^4$, $-NR^4R^{4'}$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^4R^{4'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl,

C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl; and

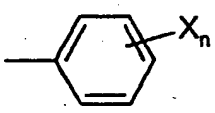
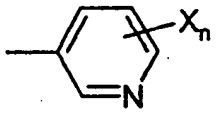
wherein R^4 and $R^{4'}$ are independently selected from the group consisting of H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl; C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

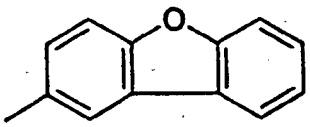
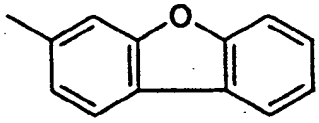
R^a is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl; and

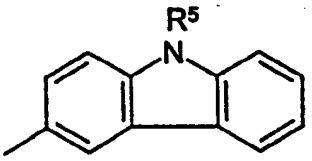
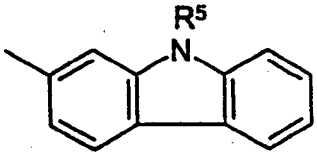
R^b is hydrogen or halogen,

R^c is hydrogen, halogen, C_1-C_{10} alkyl, up to per-halosubstituted C_1-C_{10} alkyl or combines with R^1 and the ring carbon atoms to which R^1 and R^c are bound to form a 5- or 6-membered cycloalkyl, aryl or hetaryl ring with 0-2 members selected from O, N and S.

2. A method as in claim 1, wherein B is up to a tricyclic aromatic ring structure selected from the group consisting of


and

;

which is substituted or unsubstituted by halogen, up to per-halosubstitution, and

wherein n = 0-3 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_{1-10}-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, and substituted C_1-C_{10} alkyl, substituted C_{2-10}-alkenyl, substituted C_{1-10}-alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, NO_2, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

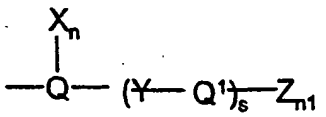
wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_{2-10}-alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is - O-, -S-, $-N(R^5)$-, $-(CH_2)_m$-, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-NR^5C(O)NR^5R^{5'}$-, $-NR^5C(O)$-, $-C(O)NR^5$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$, $-CX^a{}_2$-, -S-$(CH_2)_m$- and $-N(R^5)(CH_2)_m$-,

m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halo and optionally substituted by Z_{n1}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, =O, $-SO_2R^5$, $-SO_2NR^5R^{5'}$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl; wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, =O, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C-C_{10} heteroaryl, C_6-C_{14} aryl, C_4-C_{24} alkheteroaryl and C_7-C_{24} alkaryl.

3. A method of claim 1, wherein B is



wherein Y is selected from the group consisting of –O-, -S-, $-CH_2-$, $-SCH_2-$, $-CH_2S-$, -CH(OH)-, -C(O)-, $-CX^a_2$, $-CX^aH-$, $-CH_2O-$ and $-OCH_2-$, where X^a is halogen,

Q is a six member aromatic structure containing 0–2 nitrogen, substituted or unsubstituted by halogen, up to per-halosubstitution;

Q^1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or unsubstituted by halogen up to per-halosubstitution, and

X, Z, n and n1 are as defined in claim 1 and s is 0 or 1.

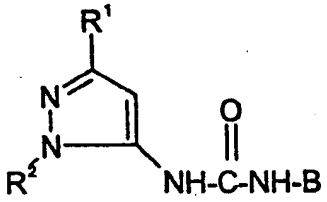
4. A method as in claim 3, wherein

Q is phenyl or pyridinyl, substituted or unsubstituted by halogen, up to per-halosubstitution,

Q^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, or -Y-Q^1 is phthalimidinyl substituted or unsubstituted by halogen up to per-halo substitution, and

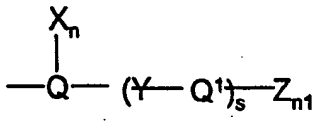
Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

5. A method as in claim 1, comprising administering a compound of the formula



wherein R^1 and R^2 and B are as defined in claim 1.

6. A method as in claim 5, wherein B is 2,3-dichlorophenyl or of the formula



wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is –O-, -S-, $-CH_2-$ or $-SCH_2$, X is CF_3, and Z is -OH, -Cl or $NHC(O)-C_pH_{2p+1}$, where p = 2-4, s = 0 or 1, n = 0 and n1 = 0 or 1.

7. A method as in claim 1 comprising administering a compound selected from the group consisting of:

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(2,3-dichlorophenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-hydroxy-phenyl)thiophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-ethylaminocarbonyl-phenyl)oxyphenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-isobutylaminocarbonyl-phenyl)thiophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)thio-3-(trifluoro-methyl)phenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(1-Methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-((4-pyridinyl)methylthio)-phenyl)urea;

N-(1-(2,2,2-Trifluoroethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-(2-Hydroxyethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-Ethoxycarbonylmethyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-(2-Cyanoethyl)-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-(3-Hydroxyphenyl)methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(1-Cyclohexyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(1-methyl3-phenyl-5-pyrazolyl)-*N'*-(3-(4-(2-methylcarbamoyl)-pyridyl)thiophenyl) urea;

N-(1-methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridyl)thiophenyl) urea;

N-(1-methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(3-(4-pyridyl)thiophenyl) urea;

N-(1-methyl-3-*tert*-butyl-5-pyrazolyl)-*N'*-(3-trifluoromethyl-4-(4-pyridylthio)phenyl) urea;

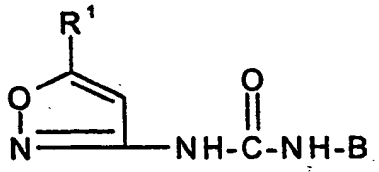
N-(3-*tert*-butyl-5-pyrazolyl)-*N'*-(3-(4-pyridyl)oxyphenyl) urea;

N-(3-*tert*-butyl-5-pyrazolyl)-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

and pharmaceutically acceptable salts thereof.

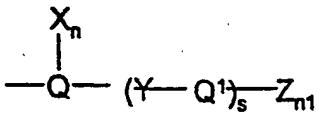
8. A method as in claim 5, wherein R^1 is t-butyl.

9. A method as in claim 1 comprising administering a compound of the formula



wherein R^1 and B are as defined in claim 1.

10. A method as in claim 9, wherein B is



wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is –O-, -S- or -CH_2, X is CF_3, Z is OH, CH_3, - O-C_pH_{2p+1}, wherein n = 2-6 or –C(O)-NH-CH_3, s = 1, n = 0 or 1 and n1 = 0 or 1.

11. A method as in claim 1 comprising administering a compound selected from the group consisting of:

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-isopropoxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-isobutoxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pentyloxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-methylaminocarbonylphenyl)-oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)thio-3-(trifluoromethyl)-phenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(3-methyl-4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(3-methyl-4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-methyl-4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-methyl-4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-(2-methylcarbamoyl)pyridyl)-oxyphenyl) urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(3-(4-(2-methylcarbamoyl)-pyridyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(4-(4-(2-carbamoyl)pyridyl)oxyphenyl) urea;

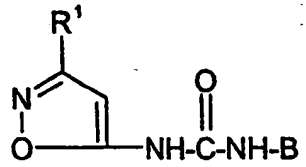
N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(3-(4-(2-carbamoyl)pyridyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(3-((4-pyridyl)fluoromethyl)phenyl) urea;

N-(5-*tert*-butyl-3-isoxazolyl)-*N'*-(3-((4-pyridyl)oxomethyl)phenyl) urea;
and pharmaceutically acceptable salts thereof.

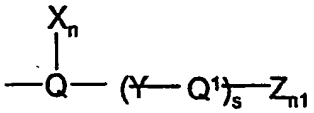
12. A method as in claim 9, wherein R^1 is t-Butyl.

13. A method as in claim 1 comprising administering a compound of the formula



wherein R^1 and B are as defined in claim 1.

14. A method as in claim 13, wherein B is 2,3-dichlorophenyl or of the formula



wherein Q is phenyl, Q^1 is phenyl, pyridinyl or benzothiazolyl, Y is –O-, –S-, $-CH_2-$ or –NH-, Z is Cl, $-CH_3$ or $-OCH_3$, s = 0 or 1, n = 0 and n1 = 0 or 1.

15. A method as in claim 13, wherein R^1 is t-butyl.

16. A method as in claim 1 comprising administering a compound selected from the group consisting of:

N-(3-Isopropyl -5-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;
N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(2,3-dichlorophenyl)urea;
N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-methoxyphenyl)aminophenyl)urea;
N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-methoxyphenyl)oxyphenyl)urea;
N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;
N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;
N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;
N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)methyl-phenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(4-(2-benzothiazolyl)-oxyphenyl)urea;

N-(3-(1-Methyl-1-ethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxy-phenyl)urea;

N-(3-(1-Methyl-1-ethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)methyl-phenyl)urea;

N-(3-cyclobutylyl-5-isoxazolyl)-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

N-(3-*tert*-butyl-5-isoxazolyl)-*N'*-(4-(4-pyridyl)thiophenyl) urea;

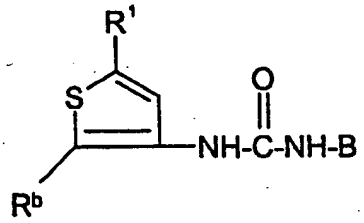
N-(3-(1-methyl-1-ethylprop-1-yl)-5-isoxazolyl)-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

N-(3-*tert*-butyl-5-isoxazolyl)-*N'*-(4-(4-pyridyl)methylphenyl) urea;

N-(3-*tert*-butyl-5-isoxazolyl)-*N'*-(4-(4-methoxyphenyl)aminophenyl) urea;

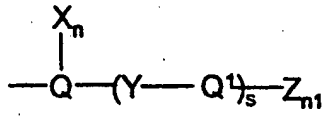
and pharmaceutically acceptable salts thereof.

17. A method as in claim 1 comprising administering a compound of the formula



wherein R^1, R^b and B are as defined in claim 1.

18. A method as in claim 17, wherein B is of the formula



wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is –O- or –S- or $–CH_2-$, Z is OH, CH_3, Cl, $-OC_2H_5$ or $–OC_3H_7$, s = 0 or 1, n = 0 and n1 = 0 or 1.

19. A method as in claim 17, wherein R^1 is t-butyl.

20. A method as in claim 17, wherein R^b is hydrogen.

21. A method as in claim 1 comprising administering a compound selected from the group consisting of:

N-(2-Bromo-5-*tert*-butyl-3-thienyl)-*N'*-(4-methylphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(2,3-dichlorophenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-ethoxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-isopropoxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(3-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-thienyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(5-*tert*-butyl-2-(1-thia-3,4-diazolyl))-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

N-(5-*tert*-butyl-2-(1-thia-3,4-diazolyl))-*N'*-(3-(4-pyridyl)thiophenyl) urea;

N-(5-*tert*-butyl-2-(1-thia-3,4-diazolyl))-*N'*-(3-(4-methoxyphenyl)oxyphenyl) urea;

N-(5-*tert*-butyl-2-(1-thia-3,4-diazolyl))-*N'*-(3-(4-methylphenyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-pyridyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-pyridyl)thiophenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-pyridyl)methylphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(2,3-dichlorophenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl) urea;

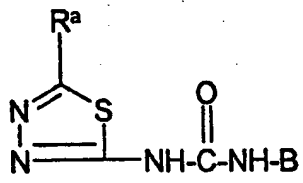
N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-methoxyphenyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-ethoxyphenyl)oxyphenyl) urea;

N-(5-*tert*-butyl-3-thienyl)-*N'*-(4-(4-isopropoxyphenyl)oxyphenyl) urea;

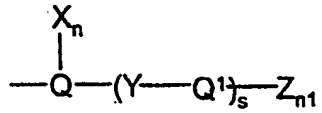
and pharmaceutically acceptable salts thereof.

22. A method as in claim 1 comprising administering a compound of the formula



wherein R^a and B are as defined in claim 1.

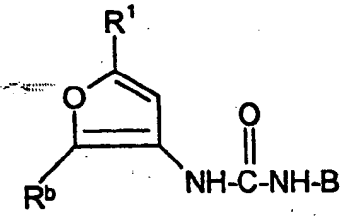
23. A method as in claim 22, wherein B is of the formula

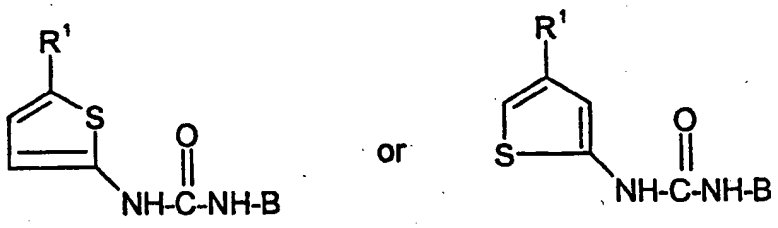


wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is –O-, –S- or CH_2-, Cl, $-OC_2H_5$ or $-OC_3H_7$, s = 0 or 1, n = 0 and n1 is 0 or 1.

24. A method as in claim 22, wherein R^a is CF_3- or t-butyl.

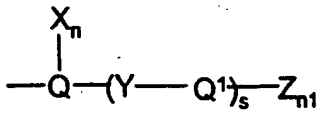
25. A method as in claim 1 comprising administering a compound of one of the formulae





wherein R^1, R^b and B are as defined in claim 1.

26. A method as in claim 25, wherein B is of the formula



wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is –O- , –S- or -CH_2-, Z is OH, CH_3, Cl, -OC_2H_5 or -OC_3H_7 , s = 0 or 1, n = 0 and n1 is 0 or 1.

27. A method as in claim 25, wherein R^1 is t-butyl.

28. A method as in claim 1, wherein the compound for formula I displays p38 activity (IC_{50}) better than 10 μm as determined by an in-vitro kinase assay.

29. A method according to claim 1, wherein the disease is mediated by a cytokine or protease regulated by p38.

30. A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit p38.

31. A method according to claim 1, comprising administering an amount of a compound of formula I effective to inhibit production of a disease-mediating cytokine or protease.

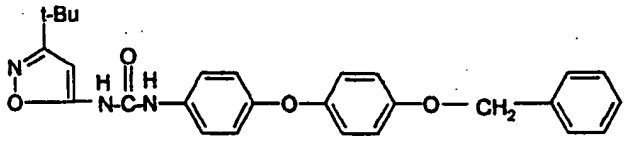
32. A method according to claim 1, wherein the disease is mediated by TNFα, MMP-1, MMP-3, IL-1, IL-6 or IL-8.

33. A method according to claim 1, wherein the disease is an inflammatory or immunomodulatory disease.

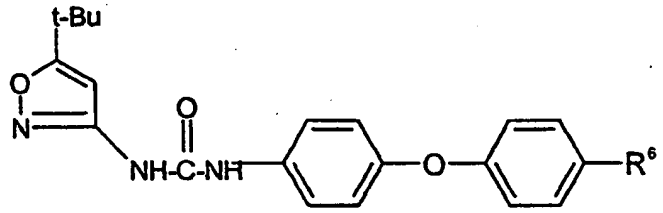
34. A method according to claim 1, wherein the disease is rheumatoid arthritis, osteoporosis, osteoarthritis, asthma, septic shock, inflammatory bowel disease, or the result of host-versus-graft reactions.

35. A compound of one of the formulae

a)

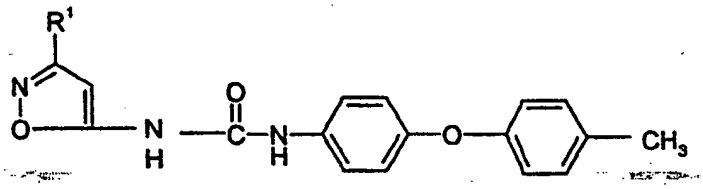


b)



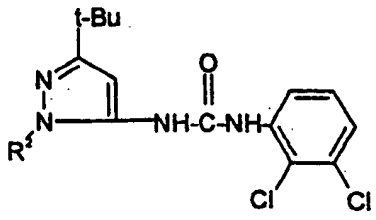
wherein R^6 is -O-CH_2–phenyl, -NH-C(O)-O-t-butyl, -O-n-pentyl , -O-n-butyl , -C(O)-$N(CH_3)_2$, -O-$CH_2CH(CH_3)_2$ or -O-n-propyl;

c)

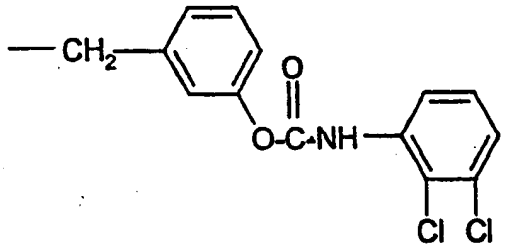


wherein R^1 is –CH_2-t-butyl;

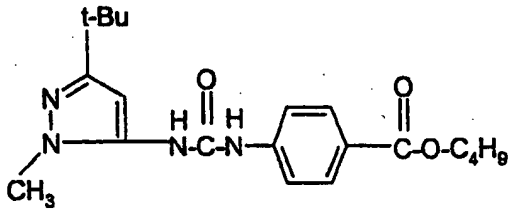
d)



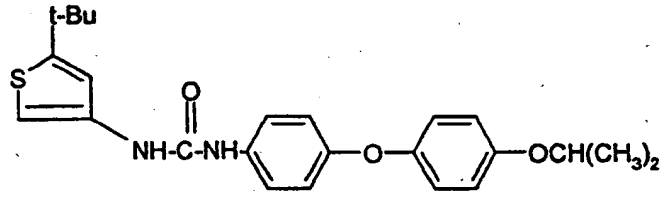
wherein R^2 is $-CH_2CF_3$, $-C_2H_4$ -OH, $-CH_2$-(3-HOC_6H_4), $-CH_2C(O)NHCH_3$, $-CH_2C(O)OC_2H_5$, $-C_2H_4CN$, or



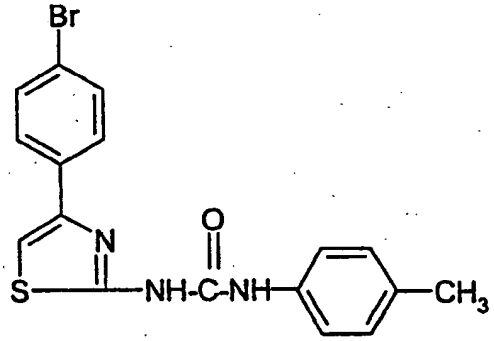
e)



f)

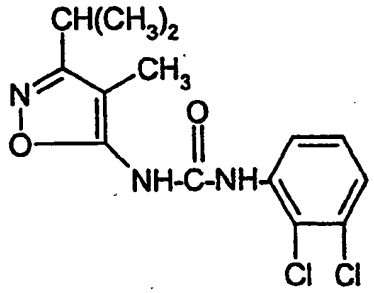


g)



or

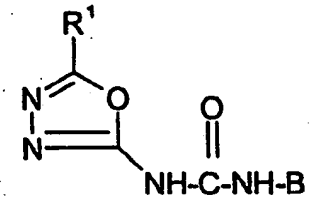
h)



and pharmaceutically acceptable salts thereof.

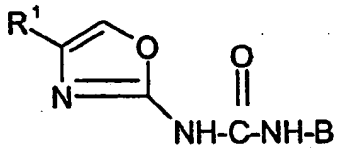
36. A pharmaceutical composition comprising a compound according to claim 35 or a pharmaceutically acceptable salt thereof and a physiologically acceptable carrier.

37. A method as in claim 1, comprising administering a compound of the formula



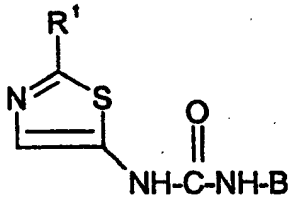
wherein R^1 and B are as defined in claim 1.

38. A method as in claim 1 comprising administering a compound of the formula



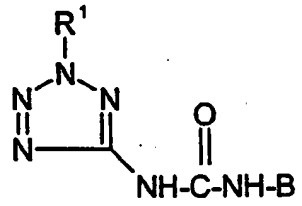
wherein R^1 and B are as defined in claim 1.

39. A method as in claim 1, comprising administering a compound of the formula



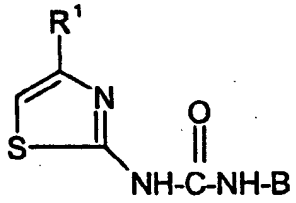
wherein R^1, R^2 and B are as defined in claim 1.

40. A method as in claim 1, comprising administering a compound of the formula



wherein R^1 and B are as defined in claim 1.

41. A method as in claim 1, comprising administering a compound of the formula



wherein R^1 and B are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26080

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/415, 31/38, 31/385, 31/35
US CL :514/407, 438, 442, 473

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/407, 438, 442, 473

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS
terms searched: arthritis, furyl, isoxazolyl, pyridine.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,319,099 A (KAMATA et al.) 07 June 1994, see entire document.	1-41

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 22 MARCH 1999	Date of mailing of the international search report 12 APR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer THEODORE J. CRIARES Telephone No. (703) 308-1235